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# ANESTHESIOLOGY CLINICS OF NORTH AMERICA

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Jonathan L. Benumof, MD, *Consulting Editor*

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## MANAGEMENT OF PATIENTS WITH MULTISYSTEM ORGAN FAILURE

Vladimir Kvetan, MD, and Jeffrey Askanazi, MD, *Guest Editors*

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# *Contents*

**Preface** ........ xi

*Vladimir Kvetan and Jeffrey Askanazi*

**Metabolic Effects of the Neuroendocrine Stress Response** ........ 1

*Ulrich Suchner and Michael M. Rothkopf*

The neuroendocrine response to stress produces profound changes in metabolism. For example, hepatic glucose output is increased while peripheral utilization of glucose is suppressed by the actions of cortisol, catecholamines, growth hormone, and glucagon. The complex endocrine events and the metabolic adjustments they induce are reviewed.

**Hematologic and Immunologic Abnormalities Associated with Multisystem Failure** ........ 23

*Janice P. Dutcher*

Hemostatic and immunologic abnormalities are characteristic of the clinical picture of patients with multisystem failure. Hemostatic abnormalities may be a result of the multisystem failure or in case of consumptive coagulopathy and microangiopathic hemolytic anemia, may be a cause of multisystem failure. The management of these abnormalities is improving and guidelines are evolving. With immunologic abnormalities, we are able to define a myriad of deficiencies and imbalances, but our ability to intervene in a meaningful way is currently limited. Nevertheless, the current explosion in interest in immune intervention promises to enhance our knowledge and hopefully our clinical management of these deficits in the critically ill patient.

**Monitoring of Metabolic Response in Multisystem Organ Failure** ........ 39

*Simon Bursztein*

There are several interpretations of the term metabolic response. This article deals primarily with the

energy metabolism monitoring of multisystem organ failure.

**Nutrition in the Acutely Ill** ........................................ 49

*Jeffrey Askanazi, Vladimir Kvetan, and Paul Goldiner*

Because of complications that developed in the use of standard nutrition principles in the ill patient, new techniques have evolved based on understanding the metabolism and interorgan relationships in hypermetabolism and organ failure. This article discusses a comparison of the metabolic changes that occur with nonstressed and stressed starvation, the importance of preoperative total parenteral nutrition, and principles for the design of appropriate regimens for postoperative total parenteral nutrition and multisystem organ failure.

**Septic Shock** ........................................ 73

*Charles Natanson and Joseph E. Parrillo*

Septic shock is a clinical syndrome produced by microorganisms, their toxins, or both, invading the blood stream of a host. Traditionally, gram-negative bacteria have been associated with septic shock, however, a wide variety of microorganisms including gram-positive bacteria, fungi, protozoa, and viruses have been implicated in initiating this syndrome. The hallmark of this disease is septicemia with cardiovascular instability, evidenced by systemic hypotension. An array of exogenous toxins and endogenous mediators may lead to progressive multisystem organ failure, through mechanisms that are still poorly understood.

**Cardiovascular Dysfunction in Multisystem Organ Failure: Focus on Septic Shock** ........................................ 87

*David Kramer, Vladimir Kvetan, Jeffrey Askanazi, and Elliott Lazar*

Sepsis is the most common clinical syndrome preceding multisystem organ failure and a frequent finding in critically ill patients. This article discusses the cardiovascular pathophysiology of septic shock.

**Hemorrhagic Shock** ........................................ 119

*Valery Bayshtok and Charles Hanf*

Hemorrhage is one of the major causes of hypovolemia. This article discusses the pathophysiology of the hemorrhagic shock state and subsequent organ failure. Also discussed is fluid resuscitation of the patient in hemorrhagic shock. Which fluids should be used? How much? What adjuncts, if any, are helpful? The final section contains recommendations for therapy.

**Pulmonary Dysfunction in Multisystem Organ Failure** .............. 135

*Greg Ruskin and Harry Ulrich*

Pulmonary dysfunction in the patient with shock and multisystem organ failure may take the form of parenchymal injury culminating in the adult respiratory distress syndrome, or abnormalities of respiratory muscle function and central drive, which result in pump failure. The clinical importance of respiratory muscle fatigue is reflected by the high incidence of hypercarbic respiratory failure despite normal lungs in the patient with shock and metabolic acidosis. In this article, aspects of both parenchymal and nonparenchymal respiratory dysfunction in the patient with shock will be addressed with a focus on issues relevant to patient management.

**Acute Renal Failure** ........................................................ 173

*Jukka Takala, Esko Ruokonen, and Aarno Kari*

Acute renal failure is a typical component of multisystem organ failure. Acute renal failure is more likely to occur in a sicker patient population now than it did before, often in conjunction with multisystem organ failure. The treatment of acute renal failure in the intensive care unit is an integral part of the comprehensive management of multisystem organ failure.

**Hepatic and Splanchnic Response in Multiorgan Failure** ............ 185

*Sylvie-Anne Bursztein-De Myttenaere and Pierre Singer*

Although the sequence of organ impairment in multisystem organ failure is variable, the gastrointestinal tract is involved fairly early, but because of the paucity of specific symptoms, the dysfunction is not immediately recognized unless particular attention is given to the problem. This article focuses on the dysfunction of the different parts of the gastrointestinal tract and the extent to which it participates in the progression of multisystem organ failure.

**Neurologic Complications of Organ System Failure** .................. 203

*Patrick A. Lasala and Frank Boehm*

Among the various organ systems, the central nervous system is unique in the degree of its depen-

dence on glucose and oxygen, and its exquisite sensitivity to their deprivation. The central nervous system is secondarily affected by a wide range of disease states and is the target of more exogenous substances than other systems. This underlines the importance of treating many of these disorders prior to central nervous system involvement.

**Modifying Systemic Responses with Anesthetic Techniques** ......... **221**

*Charles Weissman and Ingrid Hollinger*

Anesthetic agents and techniques can modify the systemic responses to surgical injury. Epidural blockade with local anesthetics in patients undergoing lower abdominal or lower extremity elective surgery can markedly attenuate the plasma levels of many of the stress hormones. It appears that it is more difficult to achieve comparable degrees of attenuation in upper abdominal surgery. The applicability of these findings to patients with multiple system failure is discussed.

**Current Status of Multisystem Organ Failure and Possible Directions for the Future** .................................................. **237**

*Christopher Bryan-Brown*

The current status of multisystem organ failure has changed little over the past few decades, but a better understanding of the mechanisms is giving the physician more therapeutic ideas to follow. The major thrust is still prevention, which is achieved by an immediate and full resuscitation of the circulation and oxygenation of the tissues, with the removal of noxious influences such as dead or severely damaged tissues and sepsis.

**Index** .................................................................. **247**

**Subscription Information** ................................ **Inside back cover**

## ERRATA

In the September 1987 issue, the author of "Neurosurgical Interventions for Chronic Pain Problems" was incorrectly listed in the table of contents as Richard B. Path. The correct name of the author is Richard B. Patt.

The author of "Postanesthetic Care of the Neurosurgcal Patient" was incorrectly listed in the table of contents as Robert C. Roselund. The correct name of the author is Robert C. Rosenlund.

## RECENT ISSUES

December 1987

**POSITIVE AIRWAY PRESSURE THERAPY: PPV AND PEEP**
Barry A. Shapiro, MD, and Roy D. Cane, MD, *Guest Editors*

September 1987

**PRACTICAL NEUROANESTHESIA**
Elizabeth A. M. Frost, MD, *Guest Editor*

June 1987

**ANESTHESIA FOR PATIENTS WITH ENDOCRINE DISEASE**
Michael F. Roizen, MD, *Guest Editor*

March 1987

**OUTPATIENT ANESTHESIA**
Herbert D. Weintraub, MD, and Marie-Louise Levy, MD, *Guest Editors*

## FORTHCOMING ISSUES

June 1988

**NEW ANESTHETIC DRUGS**
Robert J. Fragen, MD, *Guest Editor*

September 1988

**MYOCARDIAL ISCHEMIA AND PERIOPERATIVE INFARCTION**
J. G. Reves, MD, *Guest Editor*

December 1988

**CARDIAC MONITORING**
Paul G. Barash, MD, *Guest Editor*

March 1989

**MANAGEMENT OF POSTOPERATIVE PAIN**
Rollin Oden, MD, *Guest Editor*

# *Preface*

Multisystem organ failure (MSOF) is a clinical syndrome that occurs with distressing frequency in the intensive care unit. Over the last 15 years, MSOF has been thoroughly described and studied. Critical care physicians have seen numerous developments in the areas of physiologic monitoring and support systems for specific organs, which are directed at increased delivery and clearance of substrates and metabolites. These developments have increased our understanding of the pathophysiology of MSOF without significantly improving the outcome; mortality from severe MSOF remains in excess of 90 per cent. Pharmacologic intervention appears to be encountering similar barriers. The effects of both pharmacologic agents and nutrient infusions are better understood in terms of physiology outside the target area.

Successful resuscitation is possible, but frequently leaves us with patients who are organ specific cripples with dismal prognoses, especially if septic shock, respiratory and renal failure, and underlying neoplasia are involved.

The research approach that has grown up in the wake of the recent technological advances oriented toward external organ support (respirators, dialysis) is expensive and only marginally cost effective. At present, however, the most promising directions appear to be the interruption of pathways leading to end organ failure and organ specific metabolic intervention. Bedside availability of pulmonary artery, coronary sinus, hepatic vein and renal vein catheterization allow us to focus on the interaction between regional hemodynamics and substrate metabolism. The ability to infuse new substrates such as medium chain triglycerides and branched chain amino acids is now also possible.

Despite the fact that the area of critical care medicine has recently been broken up into separate certification processes, the subspecialty is multidisciplinary in nature. For this issue of *Anesthesiology Clinics of North America,* we have solicited input from specialists in the United States and abroad, as well as from collaborating physicians from our own institution. Clinical and research fellows have been actively involved in this project, since it is they who will inherit the problem and, it is hoped, contribute to its solution in the future.

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*Management of Patients with Multisystem Organ Failure*

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# Metabolic Effects of the Neuroendocrine Stress Response

*Ulrich Suchner, MD,* and Michael M. Rothkopf, MD†*

Humoral responses play an important role in the maintenance of homeostasis and in adaptation to stress. In contrast to the local response after injury, humoral responses cause general hemodynamic, metabolic, and immunologic alterations that are related to the severity of injury.

In 1942, Cuthbertson defined two phases of the metabolic response: The ebb, or shock, phase and the flow phase.[18,19] During the first several hours after injury, the ebb phase is predominant and is characterized by the restoration of circulating volume and tissue perfusion. These alterations are accompanied by a depressed metabolism and a decreased energy production manifested by decreases in oxygen consumption and heat production. This phase persists for several hours following elective operations of moderate severity and up to 2 to 3 days following severe trauma or injury. Following the ebb phase, stress metabolism switches over to the flow phase or turns into the "necrobiosis phase," the latter having been added by Stoner in 1961[98] to characterize patients with fatal outcome. Moore demonstrated in 1953[65] that the flow phase is divided into catabolic and anabolic stages. The early catabolic stage is controlled by adrenergic and adrenocorticoid hormones. Catecholamine secretion dominates during the first minutes and hours after surgery, whereas the peak cortisol secretion occurs 12 to 24 hours after surgery. This period is characterized by increased energy consumption, increased body temperature, and increased heat production. It is also accompanied by a negative nitrogen balance.

These physiologic alterations are related to an increased secretion of counterregulatory hormones and a decreased secretion and responsiveness to insulin. Furthermore, there is increased activity of the sympathetic nervous system and decreased activity of the parasympathetic nervous system.

In general, secretion of adrenal hormones returns to normal after 2 to 5 days but may be abnormal for several weeks. This so-called corticoid withdrawal phase demarcates a turning point during the course of an illness. It is associated with an increase in peristalsis, in appetite, and in spontaneous physical activity. Finally, the anabolic stage is reached, which may last sev-

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eral months after severe injuries.[65] The body is then able to undergo restoration of depleted protein and energy stores.

Stress pathophysiology can be divided into those areas dealing with fluid and electrolyte imbalances, those concerning hemodynamic alterations, and those that alter oxygen consumption, energy metabolism, and body composition. Alterations in fluid and electrolytes after trauma and sepsis and hemodynamic alterations following hemorrhage and septic shock will be addressed elsewhere in this issue. This article will attempt to focus on the metabolic response to stress, specifically the responses mediated by neurohumoral alterations.

## THE NEUROENDOCRINE RESPONSE

Stress caused by shock and trauma is mediated by a variety of neuronal and humoral reflexes, resulting in an integrated attempt by the body to meet the altered requirements of body function. The eventual goal is the reinstatement of homeostasis and adaptation to the stress condition. In attempting to reach this plateau, it is possible that the body will be unable to compensate completely or that this response will be either inadequate or overwhelming.

We will divide the neuroendocrine response into afferent and efferent limbs as a means of more completely understanding the process. This separation is somewhat artificial, since responses tend to feed back into stimuli and produce cycles of reaction and counterreaction. Nonetheless, it serves as a valid method for understanding this complex phenomenon.

### Afferent Neuronal Stimuli

The central nervous system receives afferent stimuli in stress states from the peripheral nervous system, the chemoreceptors, and the baroreceptors. The neuroendocrine response to this afferent stimulus can be viewed as the efferent limb of the system.

If the traumatized area is denervated, preventing afferent impulses from reaching the central nervous system,[24] there is no response to injury. Similarly, below the level of neuronal transection[48,49] afferent stimulus produces no response to injury. Therefore, the ability to recognize the stimulus is of critical importance to the initiation of the neuroendocrine response. This has been demonstrated in paraplegic patients,[48,49] as well as in patients receiving spinal anesthesia[70,82] during surgery.

Under epidural anesthesia, responses to growth hormone, antidiuretic hormone (ADH), cortisol, and aldosterone are inhibited. This is, of course, provided that the block is high enough to eliminate afferent somatic sensory and autonomic nervous system pathways from the area receiving surgery.[56]

The hypothalamus has a central coordinating effect on the endocrine response.[97] Removal of the anterior hypothalamus abolishes this effect, whereas removal of the cortex and those parts of the central nervous system located above the hypothalamus does not.[49] This may explain the responses to injury in patients who are under general anesthesia. Different anesthetic agents have varying effects on the neuroendocrine response, possibly because of their effect on corticohypothalamic communication.[75,76]

The secretion of gonadotropin-releasing hormone (GNRH), as well as corticotropin-releasing factor (CRF), is inhibited at the hypothalamus by the influence of opiates. Consequently, the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), and beta-endorphin are decreased, and the concentrations of testosterone and cortisol in plasma decline. In addition, thyroid-stimulation hormone (TSH) appears to be affected in some species, but the effect is not consistently found in humans. Conversely, opiates increase the serum levels of prolactin and growth hormone, presumably by reducing the dopaminergic inhibition of their release.[67,95]

Hemorrhage and sequestration of extracellular fluid (third spacing) are well-known reasons for loss of circulating body fluids after a traumatic insult. Low-pressure stretch receptors in the right atrium and high-pressure baroreceptors in the carotid arteries and aorta[3,40,46] inhibit the release of many hormones, as well as the activity of the central and sympathetic nervous systems, by toxicity. Baroreceptor activity increases if cardiac output decreases because of a diminished circulating volume. Loss of tonic inhibition results in increased release of hormones by endocrine glands via the sympathetic pathways. This is exemplified by the increased release of ACTH, vasopressin, and growth hormone from the hypophysis, as well as the increased secretion of epinephrine, norepinephrine, renin, and glucagon from peripheral sites after hypovolemic episodes.

There is a variability concerning the amount of stimulus necessary to produce a neuroendocrine response. For instance, the quantity of volume loss necessary to produce hypotension, and thus a humoral response to trauma and stress, may vary.[107] Furthermore, the time course of the stimulus and complicating factors is important in determining the response of the neuroendocrine system.[61] Recently, Chernow[14] showed differing responses of the neuroendocrine system based on the extent of abdominal surgery.

The neuroendocrine response is also mediated by pain. This important primary stimulus, which is a characteristic finding in trauma, activates nociceptive fibers, mediating the release of several hormones,[17,30,82] which include catecholamines, vasopressin, ACTH, and endogenous opiates. These hormones are also able to interact with the humoral effects mediated by hypovolemia, resulting in a potentation of the response.[5]

Nociceptive modulating systems can be activated by input from peripheral sensory nerves, but they can also be activated by the influence of higher centers. The central nervous system has a remarkable capacity to modulate the perception of pain. By electrical stimulation, for example, it could be shown that the periaqueductal gray matter produces analgesia by mechanisms that involve endogenous opiates as well as biogenic amines. There is evidence for a opioid system in the central nervous system that enhances susceptibility to painful stimuli.[110]

Fear and anxiety, which are common events during and after trauma, provoke stimulation of the limbic area, resulting in an activation of the endocrine axis involving the hypothalamus, the hypophysis, and the adrenal glands.[38] There is a direct effect of endotoxin in the hypothalamus, mediating increased release of several hormones, including growth hormone, vasopressin, ACTH, and others.[23]

There is evidence that temperature changes have an impact on the humoral response. The preoptic area of the hypothalamus is known to be sensitive to changes in core temperature. Chemoreceptors in the aortic and carotid bodies are able to detect changes in blood temperature, translating this information to distinct neuronal afferent signals in the central nervous system.[59,108] Alterations in the secretion of ACTH, vasopressin, cortisol, epinephrine, norepinephrine, aldosterone, and thyroxine have been observed.

A decrease in body temperature is known to be of significant importance in hypovolemia and burns. In animal models, for example, the release of catecholamines, ACTH, and cortisol have been shown to be diminished by hypothermia. Furthermore, adrenal sensitivity to ACTH has been found to be reduced in hypothermia.[36]

Excessive loss of heat in trauma or stress occurs when there is loss of the insulating epidermis, as seen in burns, or because of decreased thermogenesis in the liver because of blood flow abnormalities. The latter is typical during hypovolemia and hemorrhage. Inadequate peripheral vasoconstriction accounts for continuing heat loss in a number of stress situations (such as, sepsis). In contrast, elevated body temperature produces an increase in the release of ACTH, corticosteroids, and vasopressin.[108]

Variations in the content of oxygen, carbon dioxide, hydrogen, or potassium in the blood stream are detected by arterial chemoreceptors located in the aortic and carotid bodies. These chemoreceptors induce an endocrine response as well as cardiovascular and pulmonary responses.[59] The latter aspects of the response of the afferent stimuli will be discussed elsewhere in this monograph.

Although we have discussed them separately, the perception of stress leads to a summation of afferent stimuli that must be integrated in the central nervous system. This results in a balanced humoral response corresponding to the intensity of the stimulus. The specific method by which stress episodes are able to overwhelm the classic endocrine feedback regulations are unknown.[37,61,62] Furthermore, the role that the humoral response plays when interacting with other regulatory mechanisms or when inducing stress responses of its own remains complicated and unclear.

## Efferent Humoral Response

After processing the information received in the central nervous system in response to stress, the hypothalamus plays a critical role in initiating the efferent response. Hypothalamic responses travel down two pathways leading to the neuroendocrine response: the hypothalamic-pituitary axis and the autonomic-adrenal axis. The autonomic-adrenal response to stress tends to be immediate as compared with the hypothalamic-pituitary response, which has a delayed and more lasting reaction. It should be recalled that the autonomic nervous system, which is composed of both sympathetic and parasympathetic fibers, also receives input from areas other than the hypothalamus.

Increased neural activity in the central and peripheral nervous systems creates a new balance, shifting from parasympathetic to sympathetic responses. Neurotransmittor release for direct innervation and enhanced release of circulating catecholamines from the adrenal medulla mediate the strong adrenergic response.

The hypothalamus is in direct communication with all areas of the autonomic nervous system and controls the pituitary by either direct or indirect methods. The posterior pituitary hormones are synthesized in the supraoptic and paraventricular nuclei: they then travel down the tuber cinereum and are stored in the posterior pituitary gland. Releasing factors that affect the anterior pituitary gland are communicated through blood via a portal venous system.

The neuroendocrine response can be viewed as occurring in two phases. Maintainence of blood flow and energy supply to vital organs is the major goal of the first, immediate phase. The second phase induces metabolic alterations. This is expressed by the time course of the release of different hormones during periods of stress. The first-phase response releases catecholamines, ADH, renin, and aldosterone. In the second phase, metabolism is affected by secretion of counterregulatory hormones and the decreased secretion and effectiveness of insulin; the main purpose appears to be to increase the utilization of fatty acids. Mobilization of glucose and fat results in a rise in serum-free fatty acids and hyperglycemia. Increased gluconeogenesis in the liver, as well as lipolysis of fat tissue, is induced. Hypermetabolism and a relative insulin resistance are reflected by enhanced circulation of ketones and lactate.

## HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The characteristic elevation of cortisol released by the adrenal gland in periods of stress is mediated by a series of peptide hormones secreted from within the central nervous system. The hypothalamus releases CRF, mediating the release of ACTH, a 39-amino acid peptide formed in the chromophobic cells of the anterior pituitary.[111] The secretion of ACTH occurs in concert with the release of beta-endorphin because both hormones have the same precursor peptide: pre-proopiomelanocortin, (POMC), an endogenous opiate. Beta-endorphin is assumed to mediate stress-related analgesia. More details of this important hormone will be discussed further on.

ACTH stimulates the adrenal zona fasciculata, inducing an enhanced conversion of cholesterol to pregnenalone. This stimulation is mediated by an activation of adenyl cyclase and the increased production of cyclic adenosine monophosphate (cAMP).[111] ACTH is also assumed to be responsible for the release of aldosterone in concert with other stimuli (for example, angiotensin).

As already discussed, other hormones are able to interfere with neuronal relations. In particular, oxytocin, vasopressin, and angiotension potentiate the release of CRF.[35,87,112] The increase in plasma ACTH concentration has been shown to be unrelated to the severity of trauma or the amount of blood loss. Furthermore, the age of the patient or steroid concentrations during surgery have also been found to be unrelated to the extent of ACTH increase following stress.[50,70]

Increased plasma concentrations of cortisol have been shown in preoperative patients.[101] Elevated cortisol concentrations are related to the severity of injury. Thomason[101] and Clark and coworkers[16] showed that thoracic and intraabdominal operations have the greatest cortisol response. Epidural anesthesia inhibits the cortisol response to surgery by blocking sensory input to the autonomic nervous system.[26]

After trauma or surgery, plasma cortisol levels increase two to five times over basal concentrations. As much as a tenfold increase has been seen in some patients.[101] The diurnal variation of plasma cortisol is blunted by the stress of surgery.[101] Alterations in this rhythm have been detected in emotionally stimulated patients preoperatively, as well as in patients having pain postoperatively. If surgery is uncomplicated, plasma cortisol levels normally return to a baseline concentration in a period of several hours to several days.

Changes in cortisol levels during stress reflect changes in cortisol binding to its carrier protein transcortin and to a lesser extent to albumin binding. Studies have shown that transcortin binding decreases during stress, resulting in a relatively greater proportion of free cortisol than in a nonstress situation.[57]

The action of cortisol itself is not mediated by a second messenger. Because of its ability to pass through cell membranes, cortisol binds directly to cytosolic receptors, forming a migrating hormone-receptor complex. This complex interacts with DNA structures in the nucleus, modulating the transcription of messenger RNA, which results in the cellular response. RNA transcription is a most time-consuming step, causing a delay of 1 to 2 hours between the release of administration of the hormone to its onset of action.[44]

Glucocorticoids have separate metabolic effects in the liver and periphery. The overall effect is that protein is broken down in the periphery for conversion to glucose in the liver. At the same time, peripheral glucose use is inhibited, whereas peripheral fatty acid levels are increased. The liver seemingly produces new glucose from peripheral protein stores, which is intended for use in other tissues (that is, the central nervous system). The metabolic effects of cortisol are shown in Table 1.

Cortisol suppresses protein and RNA synthesis in peripheral tissues, for example, muscle, skin, adipose, lymph, and fibroblasts. Protein catabolism in some tissues are enhanced, with a subsequent release of free amino acids. This effect is greater in fast-twitch glycolytic type II muscle fibers than in type I, slow-twitch fibers. Thus, muscles such as the diaphragm, which are made up predominately of type I fibers, are less affected than are other skeletal muscles.

While peripheral proteins are being catabolized, glucocorticoids induce an increased protein and RNA synthesis in the liver. Tyrosine and tryptophan uptake is increased above that of other amino acids.

Glucocorticoids enhance hepatic glucose and glycogen production through a variety of mechanisms. Gluconeogenesis is stimulated by enhancement of the enzyme alanine aminotransferase. Similarly, phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase, two enzymes used in glycogenesis are enhanced.

Cortisol makes the liver more sensitive to the gluconeogenetic effects of glucagon and epinephrine. There is an increase in glycerol availability, suggesting induction of hepatic lipolysis. The liberated glycerol is then used for further glucogenesis.

In the periphery, insulin resistance and a reduction in the transport and use of glucose is seen following cortisol administration. Insulin levels are increased, but less so than expected for the level of blood glucose. An increase in lipolysis (direct and epinephrine-induced) follows cortisol administration with subsequent increases in free fatty acid levels. However, some tissues are less sensitive than others with respect to cortisol. Gluococorticoid excess actually produces fat deposition in the face, neck, and trunk. This is probably because of the effect of increased blood glucose and insulin levels. These tissues are apparently more responsive to insulin than to cortisol. Along with the increased lipolysis and free fatty acid levels, levels of very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) are elevated during cortisol excess.

## CATECHOLAMINES

Rapid regulation of homeostatic mechanisms during a stress period relies heavily on catecholamines, which have a half-life of only approximately 20 seconds. The catecholamines (epinephrine, norepinephrine, and dopamine) are produced either from the adrenal medulla or from nerve endings of the sympathetic nervous system. There is evidence that norepinephrine secretion predominates during physical stress, and epinephrine, predominates during emotional stress.

During major abdominal surgery, plasma catecholamine concentrations

**Table 1.** *Effect of Glucocorticoids on Metabolism.*

CARBOHYDRATE METABOLISM

- Protection of glucose-dependent functions in neuronal tissue, blood cells, and wound tissue by enhancement of glucose availability
  - Peripheral tissue
    - decreased glucose uptake in peripheral tissues resulting in an increased glucose availability with glucosuria and decreased glucose tolerance
      - decreased glucose transport in adipose tissue, skin, fibroblasts, and thymocytes
      - insulin resistance (diabetes-like state)
      - increased insulin plasma concentration
    - facilitating action on hepatic gluconeogenesis by the mobilization of amino acids from peripheral tissues
  - Liver tissue
    - increase of glucose production, glycogen synthesis and reduction in glucose metabolism
      - enhanced hepatic gluconeogenesis by
        - direct action on hepatic mitochondria (rapid onset), mediating an enhanced carboxylation of pyruvate to oxaloacetate
        - enhanced conversion of amino acids to glucose by increasing the activities of gluconeogenic enzymes (prolonged onset)
        - enhanced hepatic sensitivity to glucagon and catecholamines ("permissive action")
      - enhanced synthesis and deposition of glycogen in the liver
        - increased activity of the hepatic glycogen synthetase (activation requires the presence of insulin)
      - reduced glucose metabolism by inhibition of glycolysis and pentose-phosphate shunt
        - increased insulin resistance
        - reduced activity of glycolytic enzymes glucokinase, phosphofructokinase and pyruvate kinase

PROTEIN METABOLISM

- Enhancement of the availability of substrates for hepatic enzymes involved in the synthesis of glucose and glycogen
  - Peripheral tissue
    - metabolism of amino acids by an enhanced protein breakdown, a decreased protein synthesis, and a decreased amino acid uptake, resulting in a negative nitrogen balance with the following impact on tissues
      - reduced muscle mass
      - osteoporosis caused by reduction of the protein matrix of bone, followed by calcium losses
      - thinning of the skin
      - atrophy of hepatic tissue and inhibition of the immune system
      - decreased wound healing
  - Hepatic tissue
    - increased hepatic protein and DNA-RNA synthesis as well as an increased amino acid uptake, resulting in an enhanced de novo production of enzymes involved in gluconeogenesis; glycogen synthesis and amino acid metabolism
    - There is an increased activity of
      - pyruvate carboxylase
      - phosphoenolpyruvate carboxylase
      - fructose-1,6-diphosphatase
      - glucose-6-phosphatase
      - alanine-aminotransferase
      - glycogen-synthetase
    - increased hepatic amino acid catabolism
      - increased gluconeogenesis
      - increased activity of transaminases

**Table 1.** *Continued*

LIPID METABOLISM

- Facilitation of the effect of adipokinetic agents (permissive action)
  - enhanced lipolysis from triglycerides of adipose tissue
    - facilitation of the lipolytic response to cAMP mediated by epinephrine, norepinephrine, adipokinetic peptides of the hypophysis (ACTH, growth hormone)
    - increased plasma availability of free fatty acids, VLDL, LDL, HDL, and glycerol
  - Redistribution of body fat in the hypercorticoid state as a long-term action (Cushing's syndrome)
    - It is assumed[27a] that adipose tissue at the neck, supraclavicular area, face, and trunk responds preferentially to the lipogenic and antilipolytic actions of increased levels of insulin, whereas adipose tissue of the extremities is more sensitive to glucocorticoid-facilitated lipolytic actions of other hormones

increase.[42,99] This is particularly true in patients who respond to stress with an increase in pulse rate or blood pressure.[42,71] As with other neuroendocrine hormones, the response of catecholamines can be blocked by neuroanalgesia.[27] After termination of anesthesia, there is a repeated catecholamine response lasting several hours, especially following painful operations in which the stress state persists beyond the anesthesia.[71]

As noted previously, there are many stimuli that increase the release of catecholamines. It is known that high- and low-pressure baroreceptors are able to sense hyper- and hypotension by changing their impulse rate. Accordingly, hypoxia can be perceived by an increase in chemoreceptor activity. Pain and emotional stress stimuli are received at the limbic area of the brain. The mechanisms involved in processing this acquired information for regulating the release of the catecholamines in the central nervous system remain poorly understood. More is known about the process of mediating the action of the humoral response in the peripheral tissues. Two dopaminergic, two beta-adrenergic, and two alpha-adrenergic receptors are recognized by radioligand binding assays.[28] Both beta$_1$- and beta$_2$-adrenergic receptors as well as dopa$_1$-receptors, act by stimulating the adenylate cyclase-cAMP-protein kinase system.[28] Alpha$_2$-receptors, in contrast, act by inhibiting this system. The activation of alpha$_1$-receptors is characterized by an increased intracellular calcium content acquired by the mediation of phosphatidylinositol.[28] The dopa$_2$-receptors function via a mechanism that is not adenylate cyclase–dependent.[54]

The overall metabolic effect of catecholamine release is to increase glucose production while decreasing glucose use in the periphery. In this respect, the catecholamines have a certain similarity to glucocorticoids. In fact most of the neuroendocrine response is apparently orchestrated to achieve similiar metabolic goals. This subject will be addressed further on.

Catecholamines exert direct and indirect effects on metabolism. The indirect effects rely on mediation of other hormones released in the neuroendocrine response. In this respect, it is possible that catecholamines direct as well as respond to the neuroendocrine system. Their metabolic effects are summarized in Table 2.

The alpha-adrenergic stimulus acts indirectly on protein metabolism by increasing growth hormone secretion and suppressing insulin secretion. However, beta-adrenergic stimuli have a direct effect on amino acid release (especially alanine) from muscle.

**Table 2.** *Effects of Catecholamines on Metabolism.*

### CARBOHYDRATE METABOLISM

- Enhancement of glucose availability by the mediation of an increased glucose synthesis and a decreased glucose utilization
  - Increased glucose production and output by liver tissue
    - increased glucogenolysis (cAMP- as well as calcium-mediated)
      - stimulation of glycogen phosphorylase (rate-limiting enzyme of glycogenolysis; formation of glucose-1-phosphate from glycogen)
      - inhibition of glycogen synthetase (rate-limiting enzyme of glycogenesis; formation of glycogen from uridine diphosphate [UDP]-glucose)
    - increased gluconeogenesis (cAMP-mediated)
      - inhibition of phosphofructokinase and hexokinase by products of lipolysis and glycogenolysis
      - direct action on mitochondria, mediating an enhanced formation of phosphoenolpyruvate from lactate and amino acids (action not mediated by cAMP, similar as mentioned for cortisol)
    - decreased extra central nervous system glucose use in peripheral tissues
      - inhibition of the insulin-stimulated glucose uptake, mediated through beta$_2$ and alpha$_1$ mechanisms (insulin resistance)
      - inhibition of the release of insulin (alpha-receptor) and the stimulation of the release of glucagon (beta-receptor) reinforces the action of the counterregulatory hormones
      - increased lipolysis (beta-receptor) in peripheral tissues
      - With regard to its contribution to total glucose use, this action is overridden by the effects already mentioned

### PROTEIN METABOLISM

- Enhanced protein breakdown and amino acid release from muscle tissue, especially alanine (mediation by beta-receptors)
- Hormonal modulation by interference with the rate of secretion
  - The release of insulin from the beta cells of the pancreas is inhibited by alpha-receptor mechanisms, whereas beta-receptor stimulation increases the secretion
  - In vivo the inhibiting effect predominates strongly by mediating enforcement of the counterregulatory hormones
  - The release of glucagon from alpha cells of the pancreas is inhibited by alpha-receptor mechanisms, whereas beta-receptor stimulation increases secretion
  - In vivo the stimulating effect predominates
  - The release of renin is mediated by beta-receptor mechanisms, and the secretion of growth hormone is stimulated by the action of alpha-receptors

### LIPID METABOLISM

- Increased lipolysis, resulting in hyperlipemia provides an enhanced supply of substrate for oxidative metabolism
  - Increased activity of triglyceride lipase, mediated by beta$_1$ activation overriding an inhibiting action by alpha-receptor mechanisms in adipose and liver tissue
    - increased plasma concentration of free fatty acids and glycerol
  - increased ketogenesis
  - Inhibition of the release of insulin (alpha-receptor) and stimulation of the release of glycogen (beta-receptor) enforces the action of the counterregulatory hormones.

Catecholamines exert direct and indirect influence on the body to raise glucose production, which decreases its peripheral use. The indirect effects include suppression of insulin and stimulation of glucagon. Direct beta-adrenergic stimulation results in increased glycogenolysis, gluconeogenesis, and glycolysis. At the same time, glucose uptake in tissues other than the central nervous system are suppressed both directly by a beta-adrenergic stimulus and indirectly by suppression of insulin.

The indirect actions of catecholamines on fat metabolism are again observed with regard to suppression of insulin and stimulation of glucagon. However, direct effects are separated between alpha and beta stimuli. An $alpha_1$-stimulus suppresses lipolysis, whereas a $beta_1$-stimulus increases it. In fact $beta_1$ increases free fatty acids and glycerol levels as well as ketone production.

## GROWTH HORMONE

The secretion of growth hormone, a 191-amino acid peptide, is mediated by (GHRF). The secretion can also be diminished by an inhibiting factor, somatostatin (SRIF). Both polypeptides are released from hypothalamic areas after an adequate neuronal stimulus,[68] and they are able to control the secretion of growth hormone released from the acidophilic cells of the anterior pituitary gland.

The plasma growth hormone concentration is found to be increased, depending on the extent of trauma.[109] The hormone response is blunted by epidural and spinal anesthesia.[7,70] After approximately 1 week following major trauma, growth hormone levels return to baseline concentrations.[109]

The metabolic effects of growth hormone are shown in Table 3. These effects are mostly mediated by the action of somatomedins, a family of polypeptides with insulin-like and anti-insulin–like actions. It has also been demonstrated that growth hormone can produce most of its actions through a direct effect on cells. Somatomedin-mediated effects are thought to take place through second messengers like cAMP or guanine nucleotides.[20,80,91,106] Administration of growth hormone produces a bimodel response that is seen in all aspects of its influence on protein, carbohydrate, and fat metabolism. The initial phase in referred to as insulin-like because it mimics the effects of insulin administration. This phase last 3 to 4 hours and is followed by an anti-insulin phase that may persist for up to 4 days.

Overall, growth hormone's metabolic effects stimulate protein synthesis and favor the use of lipids over glucose for calories. The acute, insulin-like effects of growth hormone increase amino acid uptake by the cells and increase protein synthesis by stimulating the ribosome-template units. As part of the cellular response to growth hormone, RNA synthesis is increased and protein breakdown is inhibited.

Growth hormone decreases glucose use in the peripheral tissues. In the acute phase, these actions mimic insulin in that uptake of glucose is enhanced in muscle, liver, and fat. The effect on liver is most interesting, since this tissue does not require insulin in order to transport glucose. This increased uptake is followed by an increase in glucose oxidation and an increase in gluconeogenesis.

After 2 to 3 hours, growth hormone exerts an anti-insulin effect that goes far enough to induce insulin resistance. There is a strong inhibition of glucose uptake and oxidation as well as a blockade of glycogenesis.

In the early insulin-like phase, growth hormone increases conversion of glucose to fatty acids for storage. Lipogenesis is enhanced, and free fatty acid levels fall as cellular output of fatty acids declines. Inhibition of epinephrine-stimulated lipolysis has also been observed during the early stages of the growth hormone effect.

The anti-insulin phase of growth hormone administration characterizes

**Table 3.** *Effects of Growth Hormone on Metabolism*

CARBOHYDRATE METABOLISM

- Decreased rate of glucose use throughout the organism
  - Acute insulin-like actions (within 2 to 3 hours after exposure)
    - increased glucose uptake in muscle, fat, and liver cells
    - increased carbohydrate use
    - increased conversion of glucose to glycogen
  - Anti-insulin–like actions (within 3 to 48 hours after exposure)
    - decreased oxidation of glucose for free energy by fat and muscle cells
    - enhancement of glycogen deposition in muscle cells
    - diminished uptake of glucose in muscle and fat cells
    - increased gluconeogenesis in the liver
    - insulin resistence

PROTEIN METABOLISM

- Increased rate of protein synthesis throughout the organism
  - Early actions (within 2 to 3 hours after exposure)
    - increased amino acid transport through the cell membrane
    - enhanced rate of protein synthesis mediated by a direct action exerted on ribosomes
  - Late actions (within 3 to 48 hours after exposure)
    - enhancement of the transcription rate of DNA
    - decreased catabolism of protein and amino acids

LIPID METABOLISM

- Increased metabolism of fatty acids from adipose tissue and increased use of the fatty acids for energy
  - Acute insulin-like actions (within 2 to 3 hours after exposure)
    - increased conversion of glucose to fatty acids
    - increased lipogenesis
    - inhibition of epinephrine-activated lipolysis
    - decreased serum concentrations of free fatty acids
  - Anti-insulin–like actions (within 3 to 48 hours after exposure)
    - decreased conversion of glucose to fatty acids
    - increased lipolysis and decreased lipogenesis
    - increased serum concentrations of free fatty acids
    - increased oxidation of free fatty acids
    - potentiation of the lipolytic actions of catecholamines

its overall effect on fatty acid metabolism. During this phase, lipogenesis is inhibited, as is conversion of glucose to fatty acids. Lipolysis increases and serum free fatty acid levels increase as cells release newly liberated fatty acids. In association with this process, fatty acid oxygenation rises in the periphery, resulting in increased utilization.

## INSULIN

Under normal physiologic conditions, insulin secretion is controlled mostly by the blood concentration of glucose. Free fatty acid and amino acid levels also play a role in stimulating insulin. During stress episodes, the effect of circulating substrates on insulin secretion is reduced, and humoral and neuronal factors become more important. In addition, there is evidence for humoral and neuronal influence on the pancreas during stress.[12,53]

Alpha- and beta-adrenergic receptors have been found in beta-pancreatic islet cells.[84] The alpha-adrenergic receptors have been shown to inhibit insulin secretion, whereas beta-adrenergic stimulus increases it.

Elevated blood concentrations of catecholamines have been found to inhibit the release of insulin, whereas isoproterenol increased it.[25,84] Similar actions have been produced by stimulation of the sympathetic and parasympathetic innervation of the pancreas.[53,84]

Somatostatin has a direct inhibitory effect on alpha and beta cells of the pancreas.[79] As already mentioned, growth hormone has an initial stimulating effect, which is followed by inhibition.

During periods of stress, the inhibitory actions of the counterregulatory hormones decrease secretion of insulin and its effectiveness at the tissue site. Insulin resistance is induced by cortisol as well as by growth hormone, estrogen, progesterone, and parathyroid hormone.[25,79]

The generalized metabolic effect of insulin secretion is to enhance uptake of the three major substrates into cells. This is particularly true for the liver and skeletal muscle. These effects are summarized in Table 4.

Insulin secretion is stimulated by ingestion of a protein meal, and the combination of increased amino acid availability and increased insulin levels stimulates a positive protein balance. Insulin increases intracellular uptake of most amino acids and stimulates protein synthesis in muscle and liver. In addition, protein degradation, amino acid oxidation, and cellular output of amino acids decrease in the presence of physiologic concentrations of insulin. Output of the branched-chain of amino acids—leucine, isoleucine, and valine—are particularly affected by insulin secretion. Thus, increased insulin levels may be partly responsible for the alterations in amino acids observed in critically ill patients.

Insulin essentially turns off hepatic gluconeogenesis and glucose output. After a meal, glucose that is present in the portal blood is transported into the hepatocytes for glycogenesis. As much as 50 per cent of the ingested glucose is thus taken up by the liver. The liver is especially sensitive to the effects of insulin. However, it is important to recognize that insulin is not required for hepatic glucose transport. Insulin apparently increases the activity of hepatic glucokinase, increasing the liver's ability to metabolize carbohydrates. Insulin also increases the activity of 6-phosphofructo-1-kinase (PFK-1), an enzyme critical in glycolysis and glycogen synthetase, which is required for glycogen production. Insulin supresses gluconeogenesis by its rapid effect on the enzymes pyruvate carboxylase, (PEPCK), and pyruvate kinase.

Insulin exerts an anti-lipolytic effect at serum levels lower than those required for glucose transport. Increases in hepatic fatty acid synthesis require higher insulin concentrations.

Increased fat accumulation is induced by insulin via a number of mechanisms. Fatty acid oxidation is suppressed by effects on intracellular lipase and carnitine. Fatty acid transport is increased by effects on lipoprotein lipase. Glycerol formation is increased by the insulin effect on glucose. The combination of increased intracellular glycerol and fatty acids in the presence of a decrease in fat use provides optimal conditions for lipogenesis.

Insulin also exerts a profound antiketogenic action because of hepatic carnitine regulation and the stimulus of fatty acid formation. Acetylcoenzyme A (acetyl-CoA) is routed away from ketone production in favor of esterification. Insulin also induces uptake of ketones from the blood into the cell.

**Table 4.** *Effects of Insulin on Metabolism*

CARBOHYDRATE METABOLISM

- Decrease of glucose availability by promoting mechanisms enhancing storage, use, and intracellular transport
  - Increased glucose uptake in liver skeletal muscle and adipose tissue
    - increased membrane transport (skeletal muscle, adipose tissue)
  - Increased glycogenesis in liver, skeletal muscle, and adipose tissue
    - increased activity of glycogen synthetase
    - decreased activity of phosphorylase (inhibition of glycogenolysis)
  - Increased glycolysis in liver, skeletal muscle, and adipose tissue
    - increased activity of glucokinase, phosphofructokinase, and pyruvate kinase
    - decreased activity of phosphofructokinase and decreased concentration of phosphoenolpyruvate (inhibition of gluconeogenesis)

PROTEIN METABOLISM

- Stimulation of anabolic pathways for the accumulation of protein throughout the organism
  - Increased protein synthesis and reduced protein breakdown in skeletal muscle adipose tissue and liver
    - increased amino acid translation at the cell nucleus
    - decreased amino acid oxidation in the liver by inhibited gluconeogenic pathways
  - Increased amino acid uptake in skeletal muscle
    - diminished muscle release and decreased serum levels of branched-chain amino acids

LIPID METABOLISM

- Stimulation of anabolic pathways for synthesis and storage of lipids throughout the organism
  - Increased lipogenesis in liver and adipose tissue induced by insulin levels below those needed for increased glucose transport
    - increased activity of lipoprotein lipase
    - increased activity of acetyl-CoA carboxylase (liver)
    - increased synthesis of malonyl-CoA and glucose-3-phosphate
    - increased synthesis of free fatty acids (liver)
    - increased synthesis of glycerol (adipose tissue)
    - increased glycolysis-tricyclic acid cycle
    - increased pentose-phosphate shunt
  - Decreased lipid oxidation in muscle and liver tissue
    - decreased lipolysis by decreased activity of intracellular lipase in adipose tissue
  - Decreased ketogenesis in liver tissue
    - decreased carnitine and increased malonyl-CoA concentration

## GLUCAGON

Similar to the release of insulin, glucagon is released from the alpha cells to the pancreas and is also controlled by metabolites and hormones in the blood stream as well as by neural influences.[39] Under normal physiologic conditions, glucose and amino acids exert a major impact. Alpha cells are able to react to low blood glucose levels as well as to some glucogenic amino acids in a signal for release of the hormone.[103] After trauma and shock, humoral and neuronal mechanisms of hormone regulation become more important.

In contrast to insulin, sympathetic stimulation and catecholamine release further enhance release of glucogen. Beta-adrenergic receptors have been found to be present in high density within the alpha cells, explaining the pronounced adrenergic effect.[6,53]

Parasympathetic and other neuroendocrine responses, such as growth hormone, beta-endorphin, and cortisol, also enhance glucagon secretion. Insulin and somatostatin exert an inhibitory role.[31,103]

Glucagon plays a permissive role in protein metabolism. By maintaining hepatic glucose production despite elevated insulin levels, glucagon permits continued insulin secretion. This allows for continuation of insulin-induced amino acid uptake. Glucogen stimulates hepatic gluconeogenesis and glycogenolysis. It activates hepatic receptors, which mediate the release of the secondary messenger cAMP. Glucagon's effects are short-lived, lasting 30 to 60 minutes. However, the liver remains responsive to subsequent doses of glucagon, suggesting a regulatory role.

Glucagon plays an important role in ketogenesis. It induces increased fatty acid oxidation and decreased lipogenesis. The unique situation produced, in which glucose production is increased while lipogenesis is suppressed, provides a strong stimulus for the production of ketones, since excess acetyl-CoA cannot be turned into fat. The acetyl-CoA is not oxidized because of increased intercellular malonyl-CoA. This metabolite, which is increased because of glucagon's effect on glucose metabolism, is the specific inhibitor of carnitine acyltransferase I. Thus, fatty acids cannot enter mitochondria to be oxidized while malonyl-CoA levels are increased.

In comparison to the anabolic actions of insulin, glucagon exerts its effects as an antagonistic hormone, promoting fuel mobilization. In liver and adipose tissue, the metabolic actions are mediated by cAMP as a second messenger.

Glucagon and epinephrine were the first hormones in which cAMP mediation was demonstrated.[85] Therefore, it is not surprising that the metabolic effects of glucagon are similar to those of catecholamines (see Table 2), in particular with regard to their impact on carbohydrate metabolism.

The role of glucagon as a stress hormone is very well established. Its contribution to the phenomena of impaired glucose tolerance and hyperglycemia (insulin resistance) induced by stress after trauma, infection, or myocardial infarctions is considered of significant importance.[52] In addition, glucagon has hemodynamic action. When present in very high concentrations, it increases myocardial contractility, presumably because of its ability to effect the synthesis of cAMP at the myocardial cell. Recently, a spasmolytic action on the gastrointestinal tract has been demonstrated, which does not appear to be mediated by an adenylate cyclase pathway.[21] Also, an inhibitory action on the secretion of gastric acid has been reported.[15]

## ENDOGENOUS OPIATES

Three precursor molecules: POMC, preproenkephalin A (proenkephalin A), and preprodynorphin (proenkephalin B) lead to the production of compounds with endogenous opiod activity.[47,102] POMC seems to be the precursor of ACTH, beta-endorphin, and beta-lipotropin, as well as beta– and gamma–melanocyte-stimulating hormone (MSH).[102] The majority of this substance is found in high concentration in the pituitary gland.[47] It is also found in the arcuate nucleus, with diffuse interconnections in limbic and brain stem areas, such as the nucleus tractus solitarii and the nucleus commissuralis. It has also been found in pancreatic tissue. Proenkephalin A yields the pentapeptides met- and leu-enkephalin.[102] It is found in the adrenal gland, the brain, the gut, and the sympathetic ganglia. Proenkephalin B yields the peptides alpha- and beta-neoendorphin, as well as dynorphin-A and -B after cleavage. It is found in the brain, spinal cord, and gut.[102]

Proenkephalin A and B have been found in areas of the medulla oblongata that are involved in the modulation of pain. Furthermore, proenkephalin peptides are present in areas of the central nervous system that are presumed to be related to the perception of pain, such as the laminae I and II of the spinal cord and periaqueductal gray matter. They have also been found in areas that regulate autonomic and neuroendocrine functions, such as the medulla and the median eminence.

During stress episodes after trauma, surgery, or shock, ACTH and beta-endorphin, as well as met- and leu-enkephalins have been found to be increased.[60]

All the endogenous opioids act through special receptor sites designated mu, kappa, and delta.[81] In addition to their analgesic effect and their influence on the cardiovascular system, endogenous opioids have an impact on metabolism as well as in modulating the neuroendocrine response. Although their existence as neurotransmitter modulators and as neurohormones is well known, the role of endogenous opioids in neuroendocrine mediation during periods of stress is not completely understood. Beta-endorphins are known to induce a hypoglycemic effect,[104] which appears to be antagonized by naloxone. There is evidence that actions on glucose uptake in skeletal muscles[2] and hepatic gluconeogenesis[63] are involved. In addition, a stimulatory effect of beta-endorphin and met-enkephalin on the pancreatic release of insulin and glucagon has been found.[51]

Endogenous opiods may also play a role in the regulation of the secretion of several pituitary hormones. Growth hormone, vasopressin, and prolactin[66] released from the pituitary, as well as dopamine, norepinephrine, epinephrine, and cortisol secreted from the adrenal glands,[105] have been shown to be potentiated, whereas the release of ACTH is inhibited.[100] Accordingly, plasma concentrations of growth hormone and prolactin are depressed by the administration of naloxone,[4] whereas the serum levels of the LH and FSH are increased.

## RENIN-ANGIOTENSIN SYSTEM

Release of renin is known to be induced by different receptors acting via humoral as well as neuronal stimulation. Volume changes affecting vessel wall tension in the kidney produce a potent stimulus for the renin-angiotensin system.[33] Receptor sites at the macula densa located in the ascending part of the loop of Henle are activated by increasing concentrations of sodium and chloride, which triggers hormone release.[33] In addition, there are beta-adrenergic receptors as well as so-called vascular stretch receptors at the juxtaglomerular cell membrane.[33]

Trauma has been found to increase the output of renin. This effect has been shown to be abolished by epidural anesthesia.[9] Renin levles have been found to be most elevated in individuals with the lowest circulating volume.[88] In addition, ACTH, prostaglandins, vasopressin, and glucagon appear to be involved in the humoral modulation of hormone secretion.[55]

Renin is stored in an inactive form in the myoepithelial juxtaglomerular cells. After receptor stimulation, prorenin is converted into renin by proteolytic cleavage and is released into the arteriolar blood stream. An inactive precursor, angiotensinogen, which is an alpha$_2$-globulin synthesized in the liver, is released by the mediation of ACTH, glucocorticoids, estrogen, and angiotensin II. It is then converted by the effect of renin to the decapeptide angiotensin I. In the pulmonary circulation, the converting enzyme changes this structure into angiotension II by proteolytic cleavage. Angiotension II is then degraded to five different breakdown products. Angiotension III appears to be the only metabolically active of these products, stimulating the release of aldosterone from the adrenal cortex.[73] In addition to the effect of the renin-angiotension system on fluid balance and blood pressure, metabolic effects and neuronal mediation have been shown. Angiotensin II stimulates the release of aldosterone and potentiates the release of vasopressin. It also potentiates the release of CRF, which indirectly increases the secretion of ACTH. Furthermore, angiotensin II potentiates the action of ACTH. It also potentiates the release of epinephrine and increases sympathetic neurotransmitters in the autonomic nervous system.[22]

Aldosterone is released from the zona glomerulosa of the adrenal cortex after angiotensin stimulation of a calcium-dependent, cAMP-independent mechanism.[29,34] Its primary function appears to be involved with the reabsorption of sodium and the secretion of potassium and hydrogen ions in the distal tubule.

In contrast to cortisol, aldosterone acts nearly exclusively as a mineralocorticoid. It is exceedingly potent with respect to sodium retention and potassium elimination at the nephron's distal tubule. However, aldosterone has only a modest potency with regard to glycogen deposition in the liver. There are no significant effects on carbohydrate metabolism at the rate the adrenal gland secretes aldosterone or at levels that exert a maximal mineralocorticoid effect.

## ANTIDIURETIC HORMONE

ADH is synthesized by the supraoptic and paraventricular nuclei of the hypothalamus. It then passes through the pituitary stalk into the posterior pituitary at which point it is stored for secretion.

During periods of stress this nonapeptide is released from the posterior neurohypophysis. The secretion is related to the severity of stress.[77] Once again, we note that the neuroendocrine response with regard to ADH can be blocked by epidural anesthesia as well as by high doses of morphine and fentanyl.[43,83,96]

In addition to neuronal stimulus, an ADH response can be elicited by hypoglycemia, angiotension II, and an increase in plasma osmolarity as well as by reduction of the effective circulating volume.[92] Therefore, interactions with other hormones that may affect blood pressure and plasma volume may also have an impact on the regulation of ADH secretion.

The metabolic effects of ADH are predominantly limited to effects in the liver, wherein glycogenolysis and gluconeogenesis are stimulated. This process occurs through calcium-dependent, cAMP-independent mechanisms.[58,86]

## PITUITARY-THYROID AXIS

The release of thyroid hormone is governed by the anterior pituitary through TSH, which in turn is controlled by the hypothalamic hormone thyrotropin-releasing hormone (TRH). TSH is secreted by basophilic cells of the anterior pituitary. Its secretion is inhibited by a negative feedback mechanism in which circulating levels of thyroid hormone play a role.

During stress, both the stimulation and the inhibition of TSH release may be affected. For example, there are reports that the release of TSH can be inhibited by growth hormone, cortisol, and somatostatin and can be stimulated by estrogen.[32,74,90] In general, however, the effects on TSH secretion during stress appear to be of limited importance, and the production of thyroxine does not seem to be influenced. Decreasing serum concentration of TSH has been observed in the postoperative state.[1,94]

The most important influence on thyroid hormone metabolism during stress states appears to be on the conversion of thyroxine ($T_4$) to triiodothyronine ($T_3$) peripherally. During periods of acute medical illness there is an increase in the production of reverse $T_3$, a circulating hormone with reduced physiologic effect when compared with its normal analog. Concomitantly, there is a decrease of the metabolically active $T_3$. It is assumed that cortisol plays some role in the abnormal metabolism of thyroxine. These changes have been observed in a variety of medical illnesses including trauma.[1,8,11,41] A return to baseline $T_3$ concentrations generally occurs 3 to 7 days following stress.[1,13] Changes in $T_3$ and reverse $T_3$ concentrations are not inhibited by epidural anesthesia,[8] indicating an alternative pathway for the interference of this neuroendocrine function.

Despite the changes in circulating thyroid hormones, the syndrome of reverse $T_3$ is referred to as the sick euthyroid syndrome. In this state, thyroid hormone function is felt to be neither increased or decreased, and therefore therapy directed at correcting these levels is not indicated. It remains to be seen whether changes in these hormones have an effect at the cellular level.

## PITUITARY-GONADAL AXIS

LH and FSH are produced and secreted by basophilic cells of the anterior pituitary. Although very little is known about the neuronal control mechanism involved, the release of both glycopeptides consisting of identical alpha-chains but dissimiliar beta-chains, appears to be inhibited by periods of physiologic and emotional stress.[10] Interestingly, there are reports of an initial increasing concentrations of these hormones during the early stages of stress.[89]

A decreased concentration of testosterone has been noted after periods of stress. Within a week after surgery, the plasma concentration returns to normal. However, this has not been the case following severe injury, where a return to normal baseline testosterone levels may take longer.[64,69,78]

Plasma concentrations of progesterone are decreased in young women postoperatively,[93] whereas no changes in estrogen plasma concentration have been observed. This pattern may be in accordance with the catabolic response to stress, since testosterone and estrogen are both capable of exerting a metabolic effect. Testosterone has been shown to increase protein synthesis by activation of RNA polymerases I and II. This results in increased protein deposition in muscle contractile tissue.

Prolactin levels are found to be increased after injury as well as following emotional stress.[39] However, there is some uncertainty about its significance in stress metabolism. Increased release is related to the extent of surgical trauma and can also be found in minor trauma. Of note is the fact that hormone release is not inhibited by epidural anesthesia.[7] Blood levels generally return to normal within 3 days.[13,72]

Prolactin is a 198-amino acid polypeptide hormone that is structurally similar to growth hormone and is also released by the acidophilic cells of the anterior pituitary. In addition to its structural similarity, prolactin has some metabolic effects that are similar to those of growth hormone including reversible insulin resistance. The primary actions, however, are exerted on mammary development and lactation. A persistently elevated prolactin concentration has been found in patients who have had mastectomies, suggesting the presence of a negative feedback mechanism in addition to a stress response.[45] Prolactin has recently been shown to cause tachycardia and arrhythmias and has been found to affect the sodium-potassium pump.[89]

## SUMMARY

The neuroendocrine response to stress is initiated by afferent stimuli, such as pain, hemodynamic alterations, core temperature changes, circulating substrate levels, and emotional reaction. This information is processed by the central nervous system, and an efferent response is initiated through the hypothalamus. Rapid effects are mediated through the hypothalamic-autonomic-adrenal axis, whereas effects mediated through the hypothalamic-pituitary axis are slower and of longer duration.

Stimulation along these pathways produces profound changes in metabolism. Hepatic glucose output is increased, whereas peripheral use of glucose is suppressed by the actions of cortisol, catecholamines, growth hormone, and glucagon. This metabolic adjustment would appear to have been orchestrated to achieve the mobilization of peripheral fuel stores so that glucose-dependent tissues such as the central nervous system, blood cells, and wound tissue are not deprived. More remains to be learned about this important area and its effects on the outcome of critical illness.

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# Hematologic and Immunologic Abnormalities Associated with Multisystem Failure

*Janice P. Dutcher, MD**

Multisystem failure in severely ill patients is usually thought of in terms of dysfunction of "vital organs," meaning the heart, lungs, kidneys, and liver for the most part. There is another "organ," however, that is frequently adversely affected, both from the primary insult and secondarily from the dysfunction of solid organs. It is the hematopoietic and immune system, including the system of hemostasis. Although in many ways this is an artificial definition of an organ, its impairment clearly leads to major complications in seriously ill patients. The appropriate management of its dysfunction is fundamental to the management and homeostasis of other organ systems in this setting. Therefore, we will discuss disorders of the hematopoietic and immune system in the setting of multisystem failure.

## HEMATOPOIETIC COMPLICATIONS

The major hematopoietic complications in seriously ill patients, excluding hemorrhage, are related to the abnormal production of blood cells and to abnormal blood cell function. Seriously ill patients may demonstrate bone marrow failure related to sepsis, to pre-existing marrow disorders, or to drugs. Examples of factors leading to low blood counts will be discussed.

### Red Blood Cells—Aplasia

The prime example of this condition is the aplastic crisis of patients with advanced sickle cell anemia. During the disease, there is suddenly acceleration to a point at which the bone marrow can no longer keep up with the hemolytic process, and it simply stops producing. This may be precipitated by a septic episode or by a bony crisis. Folate deficiency may also be a component. Such patients must be supported through the crisis with transfusions and vitamins, but the prognosis for patients in aplastic crisis is very poor because of the other complications related to their disease. Other serious illness can lead to suppression of the bone marrow, but rarely to aplasia. However, drug-induced aplasia may occur. Examples of drugs that lead to marrow suppression are listed in Table 1.

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**Table 1.** *Critical Care Drugs Associated with Aplastic Anemia*

| |
|---|
| Amphotericin B |
| Chloramphenicol |
| Chlorothiazide |
| Cimetidine |
| Colchicine |
| Diphenylhydantoin |
| Epinephrine |
| Flucytosine |
| Methicillin |
| Penicillin |
| Phenylbutazone |
| Quinidine |
| Streptomycin |
| Sulfamethoxazole-trimethoprim |
| Sulindac |
| Indomethacin |
| Tolbutamide |
| Trimethadione |

*From* Erslev AJ: Aplastic anemia. *In* Williams WJ, Beutler E, Erslev AJ, (eds): Hematology. New York, McGraw-Hill Book Co, 1983.

### Drug-induced Hemolysis

Hemolytic anemia may develop in the setting of serious illness, apart from a component of disseminated intravascular cooagulation (DIC) or microangiopathic hemolytic anemia (MAHA), to be discussed subsequently.

Hemolysis in the critically ill patient is usually related to medication, and in view of the number of medications that these people receive, hemolytic anemia is surprisingly uncommon. Nevertheless, it must be considered as a potential problem when such patients are being evaluated for blood loss.

Table 2 lists drugs commonly used in the critical care setting that are associated with hemolytic anemia. The relative frequency is indicated.

### Acquired Neutropenia

Neutropenia may result from or be an additional complication of serious illnesses. When it arises in an already critically ill patient, the prognosis becomes extremely poor. Viral illnesses can lead to neutropenia that at

**Table 2.** *Critical Care Drugs Associated with Hemolytic Anemia*

| |
|---|
| Penicillins |
| Cephalosporins |
| Quinidine |
| Rifampin |
| Chlorpromazine |
| Isoniazid |
| Thiazides |
| Streptomycin |
| Procainamide |
| Triamterene |
| Ibuprofen |
| Erythromycin |

*From* Packman CH, Leddy JP: Drug-related immunologic injury of erythrocytes. *In* Williams WJ, Beutler E, Erslev AJ, et al (eds): Hematology. New York, McGraw-Hill Book Co, 1983.

times may be protracted, such as that associated with viral hepatitis. Even mild viral syndromes may predispose to a poorer outcome for superimposed infectious problems. A classic example of such negative synergy is in the setting of a viral syndrome preceding staphylococcal sepsis or pneumonia. Depending upon the proximity of the viral illness, severe neutropenia may accompany the staphylococcal infection, making its eradication extremely difficult. Specific viral infections frequently associated with neutropenia include influenza, poliomyelitis, and the poxes. Bacterial and protozoal infections, including brucellosis, typhoid, and malaria, may also be accompanied by severe neutropenia.

Neutropenia may also be a component of serious illnesses prior to superimposed infection. An example in which the systemic illness is more serious than the neutropenia is systemic lupus erythematosus. The neutropenia is believed to be immune mediated, with a neutrophil-specific IgG demonstrated in many cases. Although rarely a significant problem, this associated neutropenia may be connected with increased susceptibility to infection, and this is a particularly serious problem when the lupus is out of control.

Neutropenia may also be caused by a variety of medications. It obviously depends upon the clinical setting whether or not this has an impact on survival. Because patients with multisystem failure are also frequently receiving multiple medications, drug-induced neutropenia may become a significant problem. Table 3 lists many drugs pertinent to critical care that are known to affect bone marrow function, specifically producing drug-induced neutropenia.

Obviously, patients with malignant diseases receive chemotherapy and frequently become neutropenic, and the subsequent sepsis may be life threatening. They usually do not develop multisystem failure, however, so a discussion of this subgroup is beyond the scope of this article. A discussion of neutrophil function will be left to an overall discussion of host immune surveillance and function in a subsequent section of this article.

### Thrombocytopenia

A reduction in the platelet count in seriously ill patients may arise from a variety of causes. The most dangerous is the process of DIC, which will be discussed subsequently.

Additionally, thrombocytopenia may develop artifactually, as a result of dilution by multiple blood transfusions. The process of hemorrhage followed

**Table 3.** *Critical Care Drugs Associated with Neutropenia**

- Phenothiazines
- Phenylbutazone
- Sulfonamides
- Semisynthetic penicillins
- Chloramphenicol
- Indomethacin
- Cimetidine
- Quinidine
- Procainamide

*From* Finch SC: Neutrophil disorders—benign quantitative abnormalities of neutrophils. *In* Williams WJ, Beutler E, Erslev AJ, et al (eds): Hematology. New York, McGraw-Hill Book Co, 1983.

*Many additional drugs, including most antibiotics, are associated with isolated reports of neutropenia.

by unsupplemented massive red blood cell transfusions may lead to thrombocytopenia and, potentially, to bleeding. The marrow, however, is capable of response, and the numbers of platelets should regenerate extremely rapidly. Platelet transfusions may be required in the interim, however, and are frequently given prophylactically to patients who rapidly receive more than 10 to 12 units of blood. This procedure continues to be controversial.

Thrombocytopenia can be a component of a variety of illnesses, including severe systemic lupus erythematosus, Felty's syndrome, malignancy, idiopathic thrombocytopenic purpura (ITP), and thrombotic thrombocytopenic purpura (TTP). The last condition falls into the subset of consumptive coagulopathies and will be discussed separately.

Thrombocytopenia leads to a bleeding disorder characterized by microcapillary bleeding and oozing. Platelets form the first line of defense when capillary barriers are broken, and in fact help to maintain the integrity of the capillary vessel walls. There is a direct correlation between bleeding time by template test and the degree of reduction of platelet count.[24] Certain drugs are frequent offenders in thrombocytopenia (Table 4).

## Platelet Dysfunction

Probably more frequent than straightforward thrombocytopenia in the critically ill patient is the development of platelet dysfunction. This is most characteristically seen in patients with moderate to severe renal failure who have developed a uremic syndrome. Even moderate renal dysfunction with a moderately elevated creatinine level and mild acidosis that does not require dialysis will produce evidence of platelet dysfunction. A functional evaluation of platelets in uremic patients shows abnormal platelet aggregation to adenosine diphosphate (ADP), collagen, and epinephrine.[8] There is also an acquired abnormality of factor VIII.[46] There are decreased platelet nucleotides and a reduction in platelet prostaglandins, all of which impair overall platelet function by impairing their response to aggregating stimuli.[7]

In uremia, certain metabolic products are retained and are felt to contribute to platelet dysfunction. They include middle molecular weight inhibitors of glucose metabolism, serotonin, and factors released by fibrino-

**Table 4.** *Critical Care Drugs Associated with Thrombocytopenia*

- DECREASED PRODUCTION
  - Thiazides
  - Alcohol
  - Vitamin deficiency
- INCREASED DESTRUCTION
  - Quinidine
  - Nonsteroidal anti-inflammatory agents
  - Semisynthetic penicillins
  - Cephalosporins
  - Trimethoprim
  - Pentamidine
  - Streptomycin
  - Diazepam and its group
  - Diphenylhydantoin
  - Imipramine

*From* Abraham E, Chang YH: The effects of hemorrhage on nitrogen-induced lymphocyte proliferation. Circ Shock 15:141, 1985.

lysis. There may also be circulating inhibitors of thromboxane production and of aggregation, such as phenols.[7]

As stated earlier, a defect in factor VIII may be a component of uremic platelet dysfunction. It is now well known that factor VIII is made of several components and is partly responsible for normal platelet function. Von Willibrand's factor (VWF) complex is such a component and is released from endothelial cells, and VWF complex appears to be rapidly degraded in the uremic state. A recently noted phenomenon is that 1-deamino-8-D-arginine vasopressin (DDAVP), a drug originally designed to treat inappropriate antidiuretic hormone (ADH) syndrome, is capable of triggering the direct release of factor VIII–VWF complex (in the form of increased VWF multimers) from endothelium.[33] Bleeding times are clearly improved, and oozing can be improved by initiating the use of this therapeutic agent in uremic patients. Levels of factor VIII–VWF complex may increase fourfold after DDAVP administration.

The corrective effect of DDAVP lasts up to 4 hours and allows safe intervention in uremic patients when necessary. If such patients are actively bleeding, achievement of hemostasis will require frequent infusions of DDAVP. Acutely, such patients may benefit from cryoprecipitiate infusion, although this procedure remains controversial.

## HEMOSTASIS

Abnormalities of hemostasis are very common in critically ill patients as a result of imbalances of clotting and fibrinolysis and their components. They may range from abnormalities seen in the laboratory to a bleeding tendency related to hepatic or renal insufficiency to severe hemorrhagic consumptive clotting or bleeding. Major illnesses, injury, or organ dysfunction may also impair the normal balance and lead to bleeding or clotting problems, or both. Problems may arise with relation to the production of clotting factors and with their rapid use. These abnormalities will complicate the management of severely ill patients. Therefore, it is most prudent to anticipate abnormalities of coagulation in patients with multisystem failure and to monitor these patients.

### Normal Hemostasis

Normal hemostasis requires the controlled rate synthesis of a number of proteins that enzymatically interact to activate each succeeding step in the clotting process. This balance can be perturbed by endothelial damage, such as occurs in injury, triggering clotting at a site of damage; this may be beneficial. Other tissue factors may trigger clotting, such as components of tumors, which may be less helpful. Accelerated clotting and fibrinolysis occur in consumptive coagulopathies, and impaired protein synthesis by the liver may impair the coagulation process.

### Liver Disease and Coagulopathy

Critically ill patients frequently have impairment of liver function, which may be manifested in part as abnormal coagulation. Liver dysfunction may be acute and fulminant or more chronic, and the acuteness of clotting abnormalities or bleeding complications, or both, will reflect this.

The liver is an important metabolic organ and is responsible for the synthesis of all clotting factors except factor VIII. It is also responsible for synthesis of the components of the fibrinolytic system, plasminogen, protein

C, protein S, and the components of the coagulation regulatory system—antithrombin III, C-1 inhibitor, and alpha$_2$-macroglobulin. The liver also plays a critical role in the clearance of activated coagulation factors and plasminogen activators.[27,31]

Vitamin K is a necessary component of the synthesis of clotting factors II, VII, IX, and X, and in liver dysfunction reduced or abnormal vitamin K-dependent factors may be produced. Factor IX is affected less than the other vitamin K-dependent factors, and factor VII, with the shortest half-life, is most frequently affected.[38]

Factor V is produced by both the hepatocytes and the reticuloendothelial cells of the liver and so is the clotting factor least affected by hepatocellular insufficiency; nevertheless, its level is often low in severe hepatic insufficiency.

Acute liver injury may occur as a result of infection, for example, viral hepatitis or shock, or from fulminant hepatic insufficiency. In such conditions, the synthetic capacity of the liver falls to zero, and all clotting factors must be supplemented. In acute liver failure, the ability to clear activated coagulation factors is also severely impaired, and a consumptive coagulopathy (DIC) may result. Fibrin degradation products are usually elevated because they cannot be metabolized, and the clinician must attempt to distinguish ongoing DIC from poor clearance of fibrin degradation products. In critically ill patients, it is often the case that both problems are occurring.[4,19,44]

Coagulation abnormalities that show up in the laboratory and are characteristic of severe hepatic damage include hypofibrinogenemia, increased fibrin degradation products, decreased fibrinogen survival, and prolonged prothrombin time, partial thromboplastin time, and thrombin time.

Bleeding is not infrequent and is severe. Therefore, despite the potential for "fueling the fire," cryoprecipitate and fresh frozen plasma and platelets are usually necessary to partially compensate for the poor synthesis and the ongoing DIC.

### Chronic Liver Disease

The progressive loss of hepatic parenchymal cells in chronic liver disease is associated with a progressive decrease in the plasma level of all coagulation factors except factor VIII. In addition, there is impaired use of vitamin K, further decreasing the synthetic capacity. In patients with stable chronic liver dysfunction, there appears to be an ongoing low-grade DIC process.[44] Abnormal fibrinogen is also present. Thus, it is apparent that any physical, infectious, or metabolic insult that should impair the tenuous balance of liver function may trigger myriad coagulation abnormalities.

When stable chronic liver disease is perturbed by other illness, there is often little reserve in hepatic synthetic function, so the same abnormalities of coagulation factor production seen in acute liver injury may occur when such a patient is stressed. In addition, these patients often have cirrhosis and splenomegaly, which can lead to a mild to moderate thrombocytopenia caused by sequestration. There also may be platelet functional abnormalities in chronic liver disease, with characteristics of platelet storage pool deficiency.[39] Thus, both acute and chronic liver disease are frequently associated with varying degrees of DIC.

### Malnutrition and Coagulopathy

The production of vitamin K-dependent coagulation factors depends upon hepatic function but is equally dependent upon the presence of vitamin K itself. Vitamin K deficiency is associated with the development of bleeding abnormalities and is common in the critically ill patient. The expected time frame of clinical manifestations is approximately 2 weeks after cessation of vitamin K ingestion, but seriously ill patients may use existing factors much more rapidly and thus have a greater need for additional synthesis.

Vitamin K deficiency must be considered a factor in coagulopathy in any patient unable to ingest normal food or use enteral nutrition. Unless specifically supplemented with vitamin K, total parenteral nutrition will also be deficient. Malabsorption syndromes in even moderately ill patients will lead to vitamin K deficiency, as will therapy with broad-spectrum antibiotics, which eliminate the gastrointestinal bacterial flora necessary for vitamin K production.[38]

Thus, even without signs of coagulopathy, vitamin K should be supplemented in critically ill patients. When there are signs of bleeding or coagulopathy, it is essential to replace vitamin K, even as one searches for other component causes for the bleeding or coagulation abnormalities.

## Consumptive Coagulopathy

Consumptive coagulopathy (another term for DIC) may occur in association with a number of clinical problems. Liver disease is a frequent cause, as previously described. Serious infection, serious tissue damage (such as crush injury), obstetric complications, certain malignancies such as promyelocytic leukemia, and snakebite are the most frequent triggering processes.[34]

Virtually any gram-negative organism can produce severe DIC, although histopathologic documentation is usually only available in patients who die of gram-negative shock within the first 24 hours. Gram-positive infections do produce DIC, although less frequently. Purpura fulminans—with hemorrhagic bullae, hemorrhagic ischemic necrosis, and even gangrene—is rare but is associated most commonly with streptococcal infection, often scarlet fever. Waterhouse-Friderichsen syndrome is most commonly seen during meningococcal sepsis, although pneunococcal infection has also been associated. DIC has also been documented in viral and protozoal infections.

A consumptive thrombohemorrhagic syndrome is a manifestation of thrombin formation.[34] There is clotting with consumption of fibrinogen, platelets, and other coagulation factors. When there is injury to the vascular endothelium (that is, from endotoxin), activation of factor XII occurs, leading to activation of the intrinisic pathway of coagulation with subsequent activation of fibrinolysis and kinin formation. A series of mediators are then released, including prekallikrein and kallikrein inhibitors. When there is injury to tissues other than vascular endothelium, the mechanism for triggering coagulation is through factor X in the presence of factor VII. Malignant promyelocytes contain tissue thromboplastin, which activates the coagulation cascade by this mechanism.

Once the coagulation cascade is activated, several inhibitory systems are also activated, which include antithrombin III, protein C, and protein S. Unfortunately, these factors are rapidly used and exhausted by the continued coagulation stimulus. Plasmin is also activated by endothelial and tissue injury, and this substance tends to minimize the vascular obstructive and ischemic effects of consumption.

It is the balance between clotting and fibrinolysis, in addition to the actual rate of consumption of the clotting factors, that determines whether the clinical manifestations of coagulopathy will be thrombosis or severe bleeding. Clinically, the spectrum of the disorder is extremely variable, depending upon the tempo of the illness, the reversibility of the clinical problem leading to the coagulopathy, and whether the patient is able to compensate for consumption and make coagulation factors. If the major manifestations are abnormalities seen in the laboratory, the choice of treatment will depend upon whether the underlying disease is accelerating or under control.

### Acute Disseminated Intravascular Coagulation

The initial pathologic events are thrombotic, but the subsequent activation and consumption of certain coagulant proteins leads to the clinical manifestation of bleeding. There may be formation of diffuse microthrombi, affecting arterioles, capillaries, or venules. Circulatory obstruction and ischemia may occur. Of particular concern is the ongoing coagulation affecting vital organs, such as the kidneys, leading to renal dysfunction, cerebral dysfunction (more commonly seen in TTP, a syndrome at the thrombotic end of the spectrum), and perhaps pulmonary dysfunction (adult respiratory distress syndrome). The cerebral manifestations of hemorrhagic DIC (often cerebral hemorrhage) are also worrisome. All organs may be involved, and the degree of thrombosis of hemorrhage will determine the degree of dysfunction.

The diagnosis of DIC requires the measurement of fibrin degradation products, observation of signs of erythrocyte fragmentation on blood smear, and usually thrombocytopenia. Low antithrombin III levels are characteristic of DIC but are not fully specific because this event is seen in liver disease. Nevertheless, the combination of these laboratory abnormalities is highly suggestive of consumptive coagulopathy.

Clinical management includes basic life-support measures to maintain cardiac output, electrolyte balance, and end organ function. To correct most instances of DIC, the treatment is directed toward the underlying clinical problem: that is, administration of antibiotics for an endotoxin-producing infection and surgery for severely damaged tissues—crush injury, gangrene, obstetric catastrophies, and aortic aneurysm.

Antithrombotic agents should be used in specific clinical situations in which the DIC syndrome appears to be life threatening despite treatment of the underlying disorder. Heparin therapy has been used most effectively in the management of acute promyelocytic leukemia in which the treatment of the leukemia is known to exacerbate the coagulation process because of cell lysis and release of additional tissue thromboplastin from the cell granules.[13,22] Thus, by initiating heparin therapy prior to beginning antileukemic therapy, the coagulopathy can be modulated and serious bleeding prevented while the antileukemic effect takes hold. Once the majority of blasts are eradicated, the heparin can be tapered and discontinued. The value of heparin in other clinical settings is less well documented and remains highly controversial. Most experts maintain that rapid, aggressive treatment of the underlying process is more appropriate and equally effective in "turning off" the consumptive coagulopathy.

The transfusion of platelets and cryoprecipitate for fibrinogen and factors V and VIII is advised, depending on laboratory values. The goal is to maintain these values at 50 per cent of normal.[34] Although these transfusions in part "fuel the fire," in fact once the underlying disease is controlled they are extremely beneficial. Bleeding should diminish and stop during an interval of hours to several days.

Fibrinolytic inhibitors, such as epsilon-aminocaproic acid, may be used to block the accumulation of degradation products.[30] Such drugs must be used with caution, however, because they lead to further thrombosis and cause additional ischemic damage in a thrombotic coagulopathy if the patient is not first treated with heparin. Thus, the role of this type of drug is extremely limited, and the danger may outweigh the benefit.[34] The indication for use is clinical, with severe, dangerous bleeding not responding to replacement therapy.

### Liver Transplantation

Finally, the combination of hepatic failure and acute DIC is manifested in the unique syndrome caused by liver transplantation.[5] The process is well characterized, with acute and frequently severe hemostatic dysfunction beginning as soon as the poorly functioning liver is removed. There is then total loss of the ability to clear the activated coagulation factors and fibrinolytic activators that are released during surgical trauma. The severity and duration of the induced coagulopathy is directly related to the state of preservation of the transplanted liver. If the donor organ is damaged, the coagulopathy may actually worsen significantly. Similarly, the process of rejection of this or any other organ initiates a low-grade DIC.

### Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

TTP is an unusual clinical syndrome, producing both multisystem failure and coagulopathy, the primary manifestation of which is a consumptive coagulopathy. Although it is very likely to be of diverse cause, the clinical manifestations are repetitive with a relatively consistent group of problems: consumptive thrombocytopenia, MAHA, renal disease, fluctuating neurologic abnormalities, and fever.[6,15] The pathologic lesion is a hyaline thrombus occluding capillaries and precapillary arterioles. These lesions are found specifically in pancreas, adrenal glands, heart, brain, and kidneys, but with moderate sparing of lungs and liver. Hemolytic uremic syndrome (HUS) is a close relative of TTP, again with microvascular occlusive disease and prominent renal insufficiency. Its clinical syndrome includes hemolysis and renal failure, with neurologic complications being less common.

Although a defined cause for these syndromes remains difficult to determine, HUS has been associated with acute illness in the pediatric age group, with mucinous adenocarcinoma of the gastrointestinal tract in adults, and following treatment with certain chemotherapeutic drugs, such as mitomycin. It is postulated that an antigen-antibody complex with deposition in organs occurs in these settings. A cause for TTP is even less clear, but the onset has been associated with prodromal viral infections in a number of series.[15]

The management of these syndromes is first of all supportive. Specific treatment reported to yield a dramatic response in one patient may prove completely ineffective in others. A variety of specific treatments has been suggested, and combinations, either together or serially, have been used.

The most successful approach to TTP has been with blood or plasma exchange or even with plasma infusion.[36,37] It is postulated that the absence of a plasma factor contributes to thrombosis. Pooled data from three medical centers show remission rates of nearly 80 per cent using plasma exchange therapy.[21,41,43] Because the pathologic features show microthrombi and there is some indication of accelerated platelet aggregation, platelet inhibitors have been used with some success, perhaps in as many as 50 per cent of cases.[15,17] Therapy with aspirin, dipyridamole, sulfinpyrazone, and dextran has been reported. The rate of the clinical deterioration will in part determine at what level initial intervention is begun and whether antiplatelet agents or plasmapheresis, or both, are used. Corticosteroids are frequently employed; however, proof of efficacy is lacking.

Therapy for HUS has been less successful, although similar approaches have been used. Such patients may require dialysis to maintain renal function while an attempt is made to correct the disorder.

The incidence and awareness of both these clinical syndromes has been increasing and as a result the diagnosis is frequently made earlier in the course, before these patients qualify as having multisystem failure. In such patients, the coagulation abnormality precedes and causes the multisystem failure.

## IMMUNE SYSTEM ALTERATIONS IN PATIENTS WITH MULTISYSTEM FAILURE

Much of the data supporting the concept of immunosuppression in critically ill patients are the result of studies in patients suffering trauma, shock, or burns. Other observations of changes in the immune system even suggest a role for elective surgery in healthy patients as a factor in these changes. Additionally, animal studies, employing controlled variables, have demonstrated the potential causative role of trauma, shock, malnutrition, and critical illness in the development of immunosuppression. Although correlation between this immunosuppression and the development of serious infection is indirect and at times speculative, these observations and studies are intriguing and indicate potential directions for studies of clinical interventions. These data will be presented.

Components of the immune response include cellular components and serum factors. Nonspecific circulating proteins include the complement system, opsonins, and immunoglobulins, all of which require ongoing synthesis. Cellular components include macrophages and neutrophils with direct bactericidal activity. These cells recognize the foreign organism and migrate to the site of infection (chemotaxis) and ingest and destroy the invading organism (phagocytosis). Interactions with the serum proteins are also important for optimum bactericidal activity.

Lymphocytes are also important in the immunologic response to bacteria and other foreign substances. T lymphocytes have the capacity to identify foreign antigens and further stimulate an immune and bactericidal response. B lymphocytes are then able to initiate the production of new immunoglobulins that are specific for the the invading organism. The optimal function of these and other more complex interactions enables the patient to control and, hopefully, eradicate a serious infection. It appears that entire systems with lymphocytes, macrophages, neutrophils, and serum proteins are involved in optimum host defense.

Alterations in these systems have been observed in critically ill patients and animals exposed to various traumas. The clinical impact on the overall outcome in these patients is less well defined. Nevertheless, these observations may suggest a means of positive intervention in the overall management of critically ill patients.

### Nutrition

It is well documented that patients who are critically ill, including burn patients, suffer from poor nutrition. The stress associated with acute illness results in a hypermetabolic state with increased use of nutrients in a situation in which very little new nutrition is added. The proteins associated with an optimal immune response must be synthesized on an ongoing basis and may become depleted in the setting of malnutrition. Several studies have reported a decrease in the level of opsonins, which are glycoproteins that enhance bacterial phagocytosis and reticuloendothelial clearance, as well as decreased levels of complement proteins in patients with protein-calorie deficiency states. Nutritional factors may also play a role in cell-mediated immunity with depressed delayed hypersensitivity.[12,25]

### Reticuloendothelial System

The reticuloendothelial system (RES) appears to be easily damaged by acute insults such as hemorrhagic shock, trauma, and serious illness.[1,28] This is probably related to the damage that such events inflict upon the liver, which contains the largest functional RES. The degree of RES dysfunction reflects the degree of overall damage to the patient. Serum factors are an important component to overall RES function. They provide the opsonins and complement, as already described. Studies are ongoing to replete opsonins, utilizing cryoprecipitate in an attempt to restore RES function even in the face of liver damage. However, no studies have yet shown a definitive benefit in terms of preventing infection.

### Neutrophil Function

Sepsis continues to be a major cause of death following the acute insult of hemorrhagic shock and is the major cause of late death in trauma patients. Hemorrhagic shock has been suggested to have an impact on both neutrophil and lymphocyte function in reports of animal studies. The effect on neutrophil function does not appear to alter phagocytosis or the ability to ingest or kill bacteria, but there have been several reports of impaired chemotaxis of neutrophils following severe hemorrhagic insults. Davis and coworkers evaluated the neutrophils of baboons subjected to hemorrhage by assessing in vitro chemotactic response to *Escherichia coli* endotoxin-activated serum.[14] Chemotaxis was found to be severely impaired once a state of shock was achieved, and even after the animals were resuscitated. They also reported a decrease in specific granules in the neutrophils.

Christou and colleagues reported observations of the inhibition of granulocyte chemotaxis in septic patients, despite strong bacterial chemotactic stimulation.[10] They postulated that serum inhibitory factors develop in these severely ill patients, that impair granulocyte migration. Attempts are under way to identify and characterize these factors. Similar functional deficits have been observed in patients suffering blunt trauma, regardless of whether or not infection is a complication, suggesting that any serious illness or insult may affect neutrophil migratory ability.[9] In this report, improvement in neutrophil function correlated with resolution of the trauma.

### Lymphocyte Function

It has been demonstrated and well documented that the total circulating lymphocyte count falls abruptly after trauma in essentially healthy patients undergoing elective surgery.[23,42] This count depression follows the rising serum cortisol levels of a stress response to surgery, suggesting that the phenomenon of lymphocyte depression may be a result of redistribution of cells from blood to tissue.[23] There are conflicting data as to whether lymphocyte subsets are altered in trauma or serious illness, and there are some reports of an elevation of OKT8 suppressor cells, with the potential for enhanced suppressor activity and its clinical consequences.[23,32,35,45]

Evidence for enhanced suppressor cell activity has been derived from animal studies. Wang and colleagues subjected mice to limb amputation and tested lymphocyte function by proliferative assays.[45] Splenocytes demonstrated a consistently depressed proliferative capacity in response to alloantigens as well as a decreased ability to form alloreactive cytotoxic cells in mixed lymphocyte cultures. In subsequent studies, macrophages were eliminated from the culture, and lymphocyte reactivity returned to normal. Similarly, lymphocytes from traumatized animals inhibited normal lymphocytes from other animals when cocultured. Both of the latter experiments suggest an active suppressor role for both macrophages and lymphocytes in traumatized animals. Whether this can be further extrapolated to other clinical situations and to functional predisposition to infection and complications remains to be elucidated.

Additionally, early clinical observations have called attention to the loss of delayed hypersensitivity in critically ill surgical patients and in burn patients.[35,42] Although this finding is variably correlated with clinical outcome, it does indicate perturbations of the immune system in such patients, which require further definition.

Lymphocyte function may likewise be affected by hemorrhagic shock as a representation of other types of shock or serious illness. Abraham and Chang have studied the effects of hemorrhage on mitogen-induced lymphocyte proliferation.[2] In their studies, rats were depleted of 30 per cent of their blood volume; the blood was subsequently reinfused, simulating normal resuscitative efforts. Lymphocytes, obtained during and after the period of hemorrhagic shock, were evaluated for phytohemagglutinin (PHA)-induced proliferation, a functional assay of lymphocyte activation, as would be necessary to recognize any foreign antigen or to respond to other cellular or cytokine stimulation. These animals demonstrated dramatic unresponsiveness to PHA as early as 30 minutes after hemorrhage, despite blood replacement and stabilization of their clinical condition. This change in reactivity, which was normal before the hemorrhagic shock insult, suggests the potential for enhanced supressor cell activity.

Numerous chemical mediators released in stress, shock, or serious illness are also known to suppress lymphocyte activation. In addition to corticosteroids, which are elevated following acute insults, catecholamines are elevated and have been shown to depress the blastogenic response of peripheral blood lymphocytes to mitogens.[11,29] Thus, the mediators of the stress response in many critical clinical settings may also interact to suppress mediators of the immune response.

Other mediators include endorphins and methionine-enkephalin, and both have effects on lymphocyte function, some stimulatory and some inhibitory.[20,26,47] The relative importance of this in clinical situations is yet to be fully defined. It is clear, however, that this is a dynamic system with input from a number of directions and the end result is likely to be a sum of the inputs. Perhaps these mediators can be better understood and manipulated to optimize lymphocyte function and decrease the effect of suppression.

## Management

Alterations of all components of the immune system are documented in all forms of trauma, shock, and serious illness. Patients with multisystem failure have many clinical features of these conditions, often with the addition of end organ failure, sepsis, and primary problems. These abnormalities are extensive enough to make it seem logical that they have an impact on the overall outcome of such patients, but this has been difficult to demonstrate definitively, primarily because of the complexity of the clinical situation. Therefore, outlining specific interventions based on this information in an attempt to alter the ultimate outcome is even more difficult. At this time, it appears that an assessment of immune function remains an indicator of host condition, but it is difficult to use as a guide to changes in therapy. Conversely, certain interventions have been helpful in selected groups of patients—for example, the use of nutritional support in burn and trauma patients and in sepsis. Blood and plasma components may also provide factors that will enhance opsonization. Whether intervention directed toward suppressor cell mechanisms is clinically wise or potentially beneficial is a question yet to be answered. As we learn more about the immune modulations and alterations in critically ill patients, rational therapeutic stategies will, it is hoped, evolve.

## SUMMARY

Patients with multisystem failure have a grave prognosis, and other factors further impinge on the outcome. Drug-related injury to the hematopoietic system may lead to the loss of adequate red blood cells, neutrophils, or platelets. Dysfunction of these cell lines may also occur, because of drugs or disease, and will adversely affect patient recovery.

Coagulopathy is a frequent complication of multisystem failure and adds to morbidity and mortality in such patients. Coagulopathy may be a result of the failure of other organs, such as the liver or kidneys, or may be part of the ongoing disease process, such as in endotoxic shock or TTP. An understanding of the mechanisms involved and the expectation of this complication may improve the management and outcome of the patients.

Immunologic dysfunction in severely ill patients is very likely a contributor to increased morbidity and mortality. Currently, the assessment of immunologic abnormalities involves evaluation of numbers and functions of the effector cell populations. Management is currently speculative. It is therefore clear that there is much work to be done in resolving certain of the complications of multisystem failure that contribute to the problem. Knowledge and management of the hematologic and immunologic abnormalities associated with critical illness, shock, and trauma are important assets in developing an appropriate management plan, and it is hoped they will contribute to an improved outcome for such seriously ill patients.

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# Monitoring of Metabolic Response in Multisystem Organ Failure

*Simon Bursztein, MD**

The term "metabolic response" may be understood in many different ways. Indeed, several interpretations are frequently given when dealing with "metabolic response" and it is still not clear which is the real and correct meaning of "metabolic." It is used by different authors to designate the following aspects:

neuroendocrine
water and electrolytes
acid-base balance
energy expenditure or energy metabolism.

Because each of these aspects represents a wide range of problems and are discussed in other articles, this article mainly deals with the energy metabolism monitoring of multisystem organ failure.

The common features of critical states have been well studied in animal models and in severely ill patients and are characterized by:

an increase in energy expenditure[25]
an increase in nitrogen breakdown with a negative nitrogen balance[12]
an increased gluconeogenesis[24]
an insulin resistance[7]
an increased cathecholamine secretion[15]
an increase in the level of interleukin-1 and of cachectin affecting, among other things, protein and fat utilization.[6,14]

All these features are common to severely ill patients, with the magnitude varying with the severity of their illness, but only as long as they are not in shock, in a terminal or what is considered to be an irreversible state. When the situation becomes "more than life threatening" or preterminal, patients will present a reduction in oxygen consumption[17]; a reduction in energy expenditure[17]; a reduced gluconeogenesis with hypoglycemia[33]; and an alteration of protein metabolism. Multiple organ failure is usually the main aspect of critically ill patients going into an irreversible state, and this is also always complicated or partially induced by severe infection, found in close to 100 per cent of multiple organ failure patients.

Recent animal studies have shown that when severe infection is induced by peritonitis, the survivors will present hypermetabolism, whereas nonsurvivors will be hypometabolic.[17] As the authors demonstrated in this

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work, both groups had different responses to exogenous fuel supply, but the method used to provide nutrition could not be related to survival. The controversy of these two aspects of multiple organ failure, namely, the meaning of increased or decreased metabolic rate, and the response to and the influence of nutritional supply in this situation, is far from being solved.

Indeed, if for some authors multiple organ failure septic patients were always hypermetabolic,[20,25,32] for others this could not be shown.[2,27] This discrepancy in results is most probably related to the fact that the studied animals or patients differed in the type of injury, or rather in the stage at which the measurements were performed.[13] Multiple organ failure patients probably "switch" rapidly from a hypermetabolic to a hypometabolic state in which peripheral perfusion is impaired and oxygen delivery to tissue is reduced. Extremely low metabolic rates were recorded in terminal stages or in severely brain-damaged patients, but energy-expenditure measurements during the transition from a hypermetabolic to a hypometabolic state are not reported in the literature either in multiple organ failure patients or in animal experimentation. It seems that acutely ill patients may die during the hypermetabolic stage, with perhaps a very short terminal hypometabolic phase, where oxygen consumption and glucose utilization are critically reduced. More studies of energy expenditure and of metabolic response to exogenous fuel supply are necessary in order to evaluate the possibilities of influencing the evolution of energy utilization during these life-threatening situations.

Although hemodynamic and oxygen transport have been studied in multisystem organ failure patients, very little information is available concerning oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$), energy expenditure (EE), respiratory exchange ratio (RQ), and the response of these parameters to glucose, fat, or different amino acids supply. Although multiple organ failure is known to have a very poor prognosis, very little information is available concerning the influence of any therapeutic or nutritional support in these critical states.

Because monitoring means following the evolution of one or several parameters continuously or "on-line," none of the so-called metabolic data is monitored in multiple organ failure patients in the intensive care unit. The question that arises when considering "metabolic monitoring" in these critical states is, which are the parameters that could or should be followed on-line, if it is feasible and justified?

Technically, today the problem of measuring $VO_2$ and $VCO_2$ and providing a continuous display of RQ and of EE is solved. These measurements may be obtained with greater than 95 per cent accuracy. Several sophisticated tools available on the market allow satisfactory measurements after simple calibration procedures. Moreover, when the daily nitrogen excretion is derived, based on the amount of the urea in the 24-hour urinary collection, on-line measurements of fuel utilization can also be obtained.

The on-line metabolic measurements will probably indicate alterations of energy expenditure and of respiratory quotient, such as the trend of a hypermetabolic patient to become hypometabolic, pointing out an impairment of the patient's general condition. Whether this hypometabolic state with a known, very severe prognosis could be reversed by any therapeutic measures is not well established, nor is it known if nutrition of any kind or quantity would modify the metabolic behavior of these critically ill patients.

The first step in approaching this aspect of multiple organ failure is understanding the theoretical background of energy expenditure measurements in order to be able, in a second step, to have the elements that will allow an interpretation of "metabolic monitoring."

## ENERGY EXPENDITURE MEASUREMENTS

Although energy expenditure can be evaluated accurately by direct calorimetry, which measures heat loss,[22] the method of choice for acutely ill patients often connected to respirators, infusion pumps, and other devices is indirect calorimetry, based on measured heat loss, $VO_2$, $VCO_2$, and nitrogen excretion (NM).

Indirect calorimetry is based on two principles. The first principle is the law of conservation of energy. The second principle is that the energy produced in the body by the oxidation of foodstuff is equivalent to the energy produced by the combustion of these foodstuff in the bomb calorimeter. If for fat and for carbohydrate the end products in the bomb calorimeter and in the body are the same ($H_2O$ and $CO_2$), producing, respectively, 9.5 kcal and 4.1 kcal (3.74 for glucose), this is not true for protein. In the body, the end products for protein are mainly urea and some other constituents, such as creatinine, uric acid, ammonia, and 3-methylhistidine, with a production of about 4.4 kcal. In the bomb calorimeter, however, proteins are totally oxidized to $CO_2$, $H_2O$, $SO_4$, and nitrogen, with a production of about 5.7 kcal. From these measurements, stoichiometric equations can be derived for carbohydrate (dCH), protein (dP), and fat (dF) using well-established constants such as those represented in Table 1.[5,26]

Carbohydrate:

$$1 \text{ gm dCH} + 0.829 \text{ L } O_2 \rightarrow 0.829 \text{ L } CO_2 + 0.67 \text{ gm } H_2O + 4.17 \text{ kcal} \tag{1}$$

Protein:

$$1 \text{ gm dP} + 0.966 \text{ L } O_2 \rightarrow 0.782 \text{ L } CO_2 + 0.41 \text{ gm } H_2O + 4.4 \text{ kcal} \tag{2}$$

Fat:

$$1 \text{ gm dF} + 2.019 \text{ L } O_2 \rightarrow 1.427 \text{ L } CO_2 + 1.07 \text{ gm } H_2O + 9.3 \text{ kcal.} \tag{3}$$

These three equations represent fuel oxidation in the body, and the three nutrients are probably metabolized simultaneously in different proportions according to the patient's condition and many other factors, most of which are not well known.

The oxygen consumed in a certain period of time is the amount of oxygen that was used for the oxidation of given quantities of carbohydrate, protein, and fat, each of these nutrients using 0.829 L, 0.966 L, and 2.019 L of oxygen, respectively, per gram of metabolized substance. During the same period of time, carbon dioxide is produced in the amounts of 0.829 L, 0.782 L, and 1.427 L per gram of carbohydrate, protein, and fat, respectively. When the three nutrients are being metabolized there is also a heat production of 4.1 kcal for each gram of carbohydrate, 4.4 kcal for each gram of protein, and 9.3 kcal for each gram of fat.

The above-mentioned facts can be expressed by equations (4), (5), and

**Table 1.** *Standard Constants for Carbohydrates, Protein, and Fat Oxidized in the Body*

| NUTRIENT (1 gm) | $O_2$ (L) | $CO_2$ (L) | $H_2O$ (gm) | RQ | ENERGY (kcal) |
|---|---|---|---|---|---|
| Carbohydrate | | | | | |
| Starch | 0.829 | 0.829 | 0.67 | 1.0 | 4.1 |
| Glucose | 0.746 | 0.746 | 0.60 | 1.0 | 3.75 |
| Dextrose | 0.678 | 0.678 | 0.55 | 1.0 | 3.4 |
| Protein | 0.966 | 0.782 | 0.41 | 0.804 | 4.1 |
| Fat | 2.019 | 1.427 | 1.07 | 0.707 | 9.3 |

(6), representing events happening in the same period of time, and can thus be considered as a system of three equations with four unknowns. The classic method for solving these equations for dCH, dP, dF, and EE is to derive the value of dP from the urea excretion in the 24-hour urinary output. Because 30 gm of muscle is considered to contain 6.25 gm of protein, and 1 gm of NM is considered to have been produced by 6.25 gm of protein, the system of three equations with four unknowns becomes a system of four equations with four unknowns that can be solved.

$$\mathrm{VO_2\ (L)} = 0.829\ \mathrm{dCH} + 0.966\ \mathrm{dP} + 2.019\ \mathrm{dF} \tag{4}$$
$$\mathrm{VCO_2\ (L)} = 0.829\ \mathrm{dCH} + 0.782\ \mathrm{dP} + 1.427\ \mathrm{dF} \tag{5}$$
$$\mathrm{EE\ (kcal)} = 4.17\ \mathrm{dCH} + 4.4\ \mathrm{dP} + 9.3\ \mathrm{dF} \tag{6}$$
$$\mathrm{dP\ (gm)} = 6.25\ \mathrm{NM}. \tag{7}$$

Because the amount of metabolized proteins is already known from the measured urea or nitrogen in the urine, as shown in equation (7), the resolution of this system of equations allows the calculation of EE, dCH, and dF as a function of $VO_2$, $VCO_2$, and NM, as shown in equations (8), (9), and (10):

$$\mathrm{EE\ (kcal)} = 3.586\ \mathrm{VO_2} + 1.443\ \mathrm{VCO_2} - 1.180\ \mathrm{NM} \tag{8}$$
$$\mathrm{dCH\ (gm)} = 4.113\ \mathrm{VCO_2} - 2.907\ \mathrm{VO_2} - 2.544\ \mathrm{NM} \tag{9}$$
$$\mathrm{dF\ (10)} = 1.689(\mathrm{VCO_2} - \mathrm{VO_2}) - 1.943\ \mathrm{NM} \tag{10}$$

When dCH, dP, and dF are known, the water of oxidation ($H_2OM$) produced by the metabolism of dCH, dP, and dF can be calculated with the constants shown in Table 1:

$$\mathrm{H_2OM\ (gm)} = 0.67\ \mathrm{dCH} + 0.41\ \mathrm{dP} + 1.07\ \mathrm{dF}. \tag{11}$$

By solving equation (11), $H_2OM$ can also be calculated as a function of $VO_2$, $VCO_2$, and NM according to equation (12):

$$\mathrm{H_2OM\ (gm)} = 0.949\ \mathrm{VCO_2} - 0.141\ \mathrm{VO_2} - 1.220\ \mathrm{NM}. \tag{12}$$

Although $VO_2$ and $VCO_2$ could be measured by the Fick method, metabolic measurements are performed by totally noninvasive methods, consisting of volume and concentration measurements of respiratory gasses, used in the following equations:

$$\mathrm{VO_2} = (\mathrm{VI} \times \mathrm{FIO_2}) - (\mathrm{VE} \times \mathrm{FEO_2}) \tag{14}$$
$$\mathrm{VCO_2} = (\mathrm{VE} \times \mathrm{FECO_2}) - (\mathrm{VI} \times \mathrm{FICO_2}). \tag{15}$$

VI and VE are the inspired and the expired respiratory volumes, respectively, over a determined period of time; $FIO_2$ and $FEO_2$ are the inspired and expired concentrations of oxygen; and $FICO_2$ and $FECO_2$ are the inspired and expired concentrations of carbon dioxide. In equation (15), the second term is usually neglected because $FICO_2$ is close to zero. NM can be derived from measurements of urea in the 24-hour urinary excretion, as was explained previously.

Finally, a parameter that can also be recorded in metabolic monitoring is the RQ, or the ratio between $VCO_2$ and $VO_2$. The RQ can also be obtained as a function of the concentrations of $O_2$ in inspired and expired air ($FIO_2$ and $FEO_2$) and from the concentration of $CO_2$ in expired air ($FECO_2$), as indicated in equation (13):

$$\mathrm{RQ} = \frac{\mathrm{VCO_2}}{\mathrm{VO_2}} = \frac{\mathrm{FECO_2}(1 - \mathrm{FIO_2})}{\mathrm{FIO}_{2(1\,-\,\mathrm{FECO_2})} - \mathrm{FEO_2}} \tag{13}$$

In critically ill patients, the measurement of $VO_2$ is not easy, primarily when the patient requires high concentrations of $O_2$ in inspired air.[18] $VCO_2$ is easier to measure but is much more sensitive than $VO_2$ to any modification in the patient's respiratory pattern. It should also be noted that energy expenditure can only be evaluated if the amount of $CO_2$ exhaled over a given period of time corresponds to the amount of $CO_2$ produced by the metabolism over the same period of time. These difficulties can be solved if the given period of time lasts 20 to 30 minutes. Since the techniques for measuring "respiratory exchange" were described by Tissot in 1904[30] and by Douglas in 1911,[16] several improvements have been made in the measurements of $VO_2$ and $VCO_2$. About ten different tools are now available on the market, each with different problems and levels of accuracy, with some being easy to calibrate and handle and generally considered excellent.[9]

Although $VO_2$ and $VCO_2$ correspond directly to the $O_2$ consumed and to the $CO_2$ produced by the oxidation of nutrients during the measurement, the nitrogen measured in the urine does not correspond to the protein breakdown during the same period of time. There are indeed great variations of hourly urea excretions in a single day, and therefore the determination of protein breakdown from nitrogen excretion has to be performed over a 24-hour period.

It should be emphasized that for energy expenditure measurement, the factor NM may be neglected.

$$\text{EE (kcal)} = 3.586\ VO_2 = 1.443\ VCO_2 - 1.180\ \text{NM} \tag{8}$$

Assuming a $VO_2$ of 0.250 L per minute, a $VCO_2$ of 0.225 L per minute, and a NM of 0.01 gm per minute, which are in the normal range for these parameters, this would give us a EE of 1775.52 kcal per day. A 10 per cent error in $VO_2$ would cause a 7 per cent error in EE, a 10 per cent error in $VCO_2$ would cause an error of 3 per cent in EE, whereas a 100 per cent error in NM would be responsible for only a 1 per cent error in EE. For acutely ill patients presenting a hypercatabolic state with large and variable levels of protein breakdown, EE can be calculated from $VO_2$ and $VCO_2$ only, with a maximum error of no more than 2 per cent, using equation (14):[11]

$$\begin{aligned}\text{EE (kcal per day)} = {} & 3.586\ VO_2\ \text{(L per day)} \\ & + 1.443\ VCO_2\ \text{(L per day)} - 21.5.\end{aligned} \tag{14}$$

Although it is obvious that energy expenditure can be accurately measured without measuring nitrogen excretion, this information is most important for evaluating the magnitude of protein breakdown and for estimating daily nitrogen requirements.

## ENERGY EXPENDITURE ESTIMATION FROM STANDARD FORMULAS

In trying to adapt nutritional supply to needs, most dieticians and nutritionists will estimate energy expenditure from standard formulas, like those of Harris and Benedict, which are derived from sex, weight (W), height (H), and age (A) as follows:

$$\text{Men: EE} = 66.4730 + 13.7513\ W + 5.0033\ H + 6.7750\ A$$
$$\text{Women: EE} = 655.0955 + 9.5634\ W + 1.8496\ H + 4.6756\ A.$$

The values for EE obtained by these formulas are considered the basal metabolic rate or the basal energy expenditure for normal individuals and were established from measurements performed in 1919 on 136 normal men, 103 normal women, and 94 infants.[18] The values obtained with this method for normal individuals are accurate within approximately 10 per cent when compared to measured values. When corrected for the degree of stress or for the type of disease, the estimated EE is not at all adapted for critically ill patients and even less for patients with multiple organ failure because their EE values may easily vary 50 per cent or more from one patient to another or, in the same patient, from one day to the next.[23,28] On the other hand, estimated values will not vary from one day to another. In applying the Harris and Benedict formulas, the only factor that may change is weight, and even if in multiple organ failure weight is influenced by several factors like water and sodium balance, inducing over- or underhydration that will artificially change body weight, it will usually change much less than does, eventually, the EE. A better estimation could be obtained by taking into account lean body mass, but this is not common practice for clinical purposes. Estimated EE, even corrected according to patient's condition, can by no means be considered a way of monitoring metabolic response in multiple organ failure, nor for evaluating the degree of hypermetabolism or for nutritional purposes.

## INTERPRETATIONS OF $VO_2$, $VCO_2$, RQ, AND EE MEASUREMENTS

For many years, the usual way to evaluate EE was to multiply a measured value of $VO_2$ by 4.80, which is the amount of calories produced by 1 L of oxygen when consumed by a subject on a normal mixed diet. This figure of 4.80 is the mean caloric value of 1 L of oxygen when consumed by the three nutrients (Table 2). When $VO_2$ is measured within an accuracy of 5 per cent, then EE can be obtained within 10 per cent. Another way of obtaining EE from $VO_2$ is to use nomograms, such as the one suggested by Wilmore, and give an estimation of EE as a function of $VO_2$ and body surface area.[32]

If a single measurement of $VO_2$ can provide a rough evaluation of EE, the information that could be obtained with an on-line display of $VO_2$ in life-threatening situations remains to be investigated. The variations in $VO_2$ are correlated to those in EE in all situations except after a load in carbohydrates, where an excess of lipogenesis over lipolysis, or a net positive fat balance, may produce increased EE without a parallel increase in $VO_2$.[10]

If the error in $VCO_2$ measurement is smaller than the error made in $VO_2$, calculating EE from $VCO_2$ alone will induce a much greater error. The caloric value of 1 L of $CO_2$, if calculated as the mean of the calories produced by each of the nutrients, would be 4.33 kcal. If, for oxygen, the extreme caloric values are close, 4.486 kcal for protein and 5.047 kcal for carbohydrate per L of $O_2$, for $CO_2$ these extreme values are not as close, 5.047 kcal for carbohydrate and 6.63 kcal for fat per L of $CO_2$, explaining the inaccuracy in deriving EE from $VCO_2$ alone (Table 2).

**Table 2.** *Caloric Values of Oxygen and Carbon Dioxide*

| | CARBOHYDRATE | PROTEIN | FAT |
|---|---|---|---|
| Caloric value of 1 L of $O_2$(kcal/L) | 5.047 | 4.486 | 4.69 |
| Caloric value of 1 L of $CO_2$(kcal/L) | 5.05 | 5.68 | 6.63 |

The $VCO_2$ measurement alone should not be used for EE evaluation because it has a much greater variability related to food intake than $VO_2$. It is a well-known aspect of carbohydrate administration that it increases $VCO_2$ substantially and that in borderline respiratory failure patients it can, by increasing alveolar ventilation, increase the work of breathing and prevent weaning from artificial ventilation.[1] Another problem related to $VCO_2$ is that, the stores of $CO_2$ being very much greater than those of $O_2$, there may be some discrepancies between the $CO_2$ produced by the metabolism and the measurement of exhaled $CO_2$. When both $VO_2$ and $VCO_2$ can be measured, more extensive metabolic data can be derived, as described previously.

Finally, the on-line measurement of RQ can also give us some important information about the patient's metabolic condition. The values for RQ are well known for the different nutrients (Table 3):

When amino acids are converted to glucose by the process of gluconeogenesis, the RQ is equal to 1, and when fatty acids are converted into ketone bodies, the RQ is 0. It is obvious that usually all the metabolic patterns are present at the same time, but in different proportions and with a variable intensity that will determine the measured value of RQ. When the RQ is close to 1.0, it proves that the main nutrient utilized is carbohydrate. When the RQ is close to 0.7, it shows that the main nutrient utilized is fat, and if the RQ is below 0.7, it indicates formation and excretion of incompletely oxidized products like ketone bodies. When the RQ is around 0.8, there is a problem, because it may theoretically be due to the fact that the main nutrient utilized is protein or that there is a balanced utilization of all three nutrients. When the RQ is above 1.0, assuming that the patient is not hyperventilating, we may assume that the patient is in net positive fat balance, or that the lipogenesis from sugar is greater than is lipolysis.

## PRACTICAL IMPLICATIONS AND CONCLUSIONS

Multiple system organ failure is a syndrome that was identified about 15 years ago,[4,25] when life-support techniques became more efficient in patients that would have previously died of progressive cardiopulmonary failure.[19]

Monitoring of metabolic response in patients with multiple organ failure is not yet performed at the bedside of these patients. Little information is available on the pattern of hypermetabolic patients becoming suddenly or progressively hypometabolic and how they respond to different kinds of nutritional treatments. Although these patients need nutritional support, they seem resistant to nutrition. Barlett showed that there was a

**Table 3.** *Respiratory Quotient (RQ) Values for Selected Nutrients*

| NUTRIENT | RQ |
|---|---|
| Carbohydrate | 1.0 |
| Protein | 0.8 |
| Fat | 0.7 |
| Conversion of carbohydrate to fat | 8.0 |
| Pyruvic acid, glycuronic acid | 1.2 |
| Ethyl alcohol | 0.667 |

correlation between cumulative negative caloric balance and mortality rate in multiple organ failure patients. Indeed, patients that presented a cumulative negative caloric balance of 10,000 kcal over 4 to 6 days had a very high mortality rate; this kind of negative caloric balance often happens in postinjury or surgical patients kept in semistarvation.[3] Having noticed a serious increase in leucine and in isoleucine catabolism followed by an increase in catabolism of all other amino acid, some authors suggest providing patients in multiple organ failure with about 3000 kcal per day and high doses of proteins (2 to 3 gm per day) containing a high proportion of branched chain amino acids. These proteins should be administered enterally in order to promote protein synthesis in the cells of the gut mucosa and in the liver rather than in the muscle, which is enhanced when amino acids and branched chain amino acids are administered by the parenteral route.[19]

Increased mixed venous oxygenation with decreased $VO_2$ in severely ill patients was described by Border 20 years ago.[8] This kind of information that metabolic monitoring may supply, with, at the same time, EE and fuel utilization, could improve our understanding of what may be considered as the "acute metabolic failure" of multisystem organ failure. In patients with circulatory failure and reduced oxygen delivery, there is usually no reduction of ATP demands, and up to a certain point the "Pasteur effect," by which the rates of glucose and of oxygen consumption are inversely related, is an adaptative mechanism.[21] Unfortunately, the mechanism of "metabolic arrest" present in some diving animals, high altitude animals and invertebrates at risk of total anoxia for certain periods of time cannot yet be implemented in human beings with multiple organ failure.

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# Nutrition in the Acutely Ill

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Nutritional support was introduced into clinical medicine about 20 years ago. Its principles were derived from those of the agriculture field and starvation studies and focused on rebuilding muscle protein tissue. The restoration of organ function was a secondary aim, with nutritional requirements being derived from well human beings. The gold standard for success emphasized lean body mass, nitrogen balance, and visceral protein synthesis. Glucose was used as the primary fuel; a nonprotein calorie per nitrogen ratio of more than 150 per L was used, and protein loads of 1 gm per kg per day were the norm.

In the modern surgical intensive care unit, a new type of patient with catabolism and hypermetabolism and a propensity to develop progressive organ failure syndrome emerged. Initially, it seemed reasonable to use the same principles as those derived from refeeding the malnourished, unstressed patient because depletion of protein was a prominent manifestation of both problems. It was a logical step to apply nutritional support principles to these patients.

Because of complications that developed in the use of standard nutrition principles in the ill patient, new techniques have evolved based on understanding the metabolism and interorgan relationships in hypermetabolism and organ failure. These techniques focus on the support of organ structure and function, the elimination of substrate-limited metabolism, and the facilitation of metabolic pathways, use techniques of reduced glucose loads, increased fat, and amino acid loads, and have begun to use efficacy criteria that focus on organ structure and function.

This article outlines these principles and is divided into three main sections: (1) a comparison of the metabolic changes that occur with nonstressed and stressed starvation; (2) the importance of preoperative total parenteral nutrition (TPN); and (3) principles for the design of appropriate regimens for postoperative TPN and multisystem organ failure. To provide a background for the discussions of parenteral nutrition before and after injury, we will first discuss the metabolic changes that occur following starvation in normal subjects and the effect of infusing nutrients, and then address the differences that develop in response to starvation in the stressed state.

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In the section on preoperative TPN, the importance of adequately preparing the patient for surgery from a nutritional point of view is emphasized. For elective surgical procedures, the data suggest that the procedure be cancelled unless the patient is in satisfactory nutritional condition. In the section on postoperative nutritional support, the focus is on designing an optimal nutritional regimen in the stressed individual. Problems such as nutritional support for acute renal failure and acute hepatic failure are not discussed.

## METABOLIC RESPONSE TO STARVATION

During periods of starvation in normal humans, a sequence of responses develops that is aimed primarily at overall fuel conservation, with particular emphasis on preservation of body protein. During a fast there is a decrease in energy expenditure. A decrease in glucose utilization by the central nervous system (CNS) is accompanied by increasing oxidation of ketones for energy. There is a decrease in gluconeogenesis accompanied by a decrease in protein catabolism. Fat is mobilized from adipose tissue to meet energy demands and is also utilized by the liver for ketone production. In the stressed patient, the responses that develop are aimed at providing high circulating levels of substrates, particularly glucose. Preservation of body-tissue stores does not appear to be a primary consideration under these conditions.

## STARVATION IN THE NONSTRESSED STATE

Cahill[16] calculated that during the first day of starvation, a normal man weighing 70 kg used 75 gm of protein, 160 gm of adipose tissue triglyceride, and most of his liver glycogen stores, as the liver produces 180 gm of glucose. Continued fuel utilization (particularly oxidation of protein) at these rates would lead to death in a matter of weeks.[17] This does not occur because the body undergoes a wide variety of adaptations to reduce its dependence on glucose, which is synthesized primarily from muscle protein.

The production of glucose from a variety of precursors is an important adaptation during a brief fast. In a longer fast, however, production of glucose from amino acids (AAs) does not continue at these rates; instead, the fasted organism increases its oxidation of fat. The response to starvation can therefore be divided into two stages[31]: an early phase lasting approximately 1 week, and a later stage lasting 506 weeks. During the first days of a fast, when levels of insulin are decreased and levels of glucagon are increased,[17,54,65] the excretion of 12 to 14 gm of nitrogen (N) per day, the muscle release and splanchnic uptake of AA, and the continued release of glucose are evidence of gluconeogenesis. Hepatic production and brain oxidation of ketones increase and gluconeogenesis from AA decreases. Muscle uptake of glucose also decreased during a fast.[66] As substrate availability is thought to limit hepatic gluconeogenesis,[2,31,53] the decreased release of muscle AA, especially alanine, is thought to be important in protein sparing.

## EFFECT OF NUTRIENTS ON REVERSING THE FASTED STATE

When Gamble[33] investigated life raft rations to determine the optimal nutrient intake for survival at sea, he found that 100 gm of glucose per day decreased urinary water loss by eliminating the urinary excretion of ketone bodies in fasted volunteers. Further experiments on the effect of a 6-day fast demonstrated that while both 100 gm and 200 gm of glucose completely abolished the urinary excretion of ketones, maximal protein sparing was obtained with 100 gm of glucose per day. The addition of egg powder did not significantly alter protein balance; this suggests that, with insufficient caloric intake, protein is used as an energy source.

Aoki et al[1] have also studied the ability of small doses of glucose to decrease protein losses. They found that 150 gm of glucose a day (37.5 gm consumed every 6 hours) for 7 days in three otherwise-fasted, obese women appeared to diminish hepatic glucose production (as evidenced by a decrease in urea production), while ammonia formation and the excretion of ketoacids were depressed despite the gradual transition to a fasted state. When the subjects were starved for 3 weeks and again fed these glucose meals for 7 days, the investigators observed that small amounts of glucose consumed late in starvation appear to conserve protein by decreasing ammonia formation, probably as a result of decreasing blood ketone levels and excretion of the ketones.

Extensive work has been conducted on the effect of glucose, fat, and protein on N balance in the fasted state. Glucose given alone[64,88] was shown to decrease the negative N balance seen in starvation alone. In these studies glucose was given intravenously to otherwise-fasted male subjects for 8 days in 2 doses (150 to 200 gm per day and 600 to 700 gm per day). By the seventh day, total urinary N (TUN) had decreased in both groups; levels of TUN were lower in the high-glucose group than in the low-glucose group, but in both groups these levels were lower than those seen in the starved control group.[17] Plasma glucose levels were higher in those subjects receiving the high dose of glucose, but in both cases remained within normal levels during the infusion period. The rise in plasma ketone levels seen in the starved state was completely inhibited by both doses of glucose. Plasma concentrations of most AAs were decreased in both conditions. However, while alanine levels were decreased in the low-glucose group, they were increased in the high-glucose group. This may indicate decreased gluconeogenesis from alanine.

The ability of fat to reduce negative N balance has also been studied. It is generally felt that carbohydrate in small quantities (less than 500 kcal per day) has an N-sparing effect not shared by fat.[29] However, it is necessary to separate the effect of fatty acids from the gluconeogenic precursor, glycerol. Brennan et al[80] infused subjects, divided into two groups, with either Intralipid (a fat source that contains 100 gm per L soybean oil, 12 gm per L phospholipids, and 25 gm per L free glycerol) or the same amount of glycerol received in that amount of Intralipid. In both groups, blood glucose levels decreased during the first 4 days then increased to control levels during the final 4 days. Serum triglyceride (TG) levels were elevated during the Intralipid infusion, free fatty acid (FFA) levels were elevated throughout the Intralipid study to greater than fasting levels, and glycerol levels were higher during the glycerol infusion. Ketone body levels were rapidly elevated by Intralipid infusion and were mildly elevated in the group receiving glycerol. These levels were less than that seen in starvation by day eight. Levels of urinary N excretion, for both groups, were comparable with those seen when glucose is infused, and were lower than in the starved state. On a short-term basis (8 days), Intralipid reduced the negative N balance seen during fasting, but appeared to do so as a function of the glycerol component of the infusion. Wolfe et al[88] suggested that TGs are being mobilized or utilized at a maximal rate during this time and that further addition of fat does not improve the situation.

## THE STRESS RESPONSE

The metabolic response to stress is characterized by hypermetabolism, hyperglycemia, and hypercatabolism. This sequence provides high circulating substrates at the expense of body-tissue stores. In injured patients, glucose is required by the wound, the CNS, and both red and white blood cells. Because glucose stores are limited, this glucose must be synthesized from body protein stores. Increased fat mobilization and oxidation occur to meet the increased energy demands of tissues not dependent on glucose, which appear to utilize fat preferentially as an energy source, so that circulating glucose can be preserved for the wound and the CNS.

## ENERGY METABOLISM IN STRESS

Cuthbertson[22,23] and coworker Tilstone divided the postinjury response into the "ebb" and "flow" states. During the ebb, or shock phase, metabolic rate (measured by $O_2$ consumption-indirect calorimetry) is depressed, body temperature is lowered, and the volume of circulating blood is reduced. The flow phase, or period of increased metabolic activity, follows after a day or two. Cuthbertson noted an increase in urinary N, sulfur (S), phosphorous, potassium (K), magnesium, and creatinine paralleling the period of increased $O_2$ consumption. The N excretion increased to levels as high as 23 gm per day. Maximum excretion generally occurred between the 4th and 8th day after both bone and nonbone injury. The N:S and N:K ratios and extent of N loss indicated that the N was derived primarily from muscle breakdown. Cuthbertson also noted that N excretion was increased as a function of the severity of the trauma unless the patient was already depleted, in which case the response was attenuated.

Using a system designed to measure gas exchange continuously, Kinney et al[40] established ranges of resting energy expenditure (REE) in healthy volunteers and in patients with different types of trauma. Predicted REE can be obtained from tables that take into account height, weight, age, and sex. The REE is equal to the basal metabolic rate increased by 10 per cent to account for the specific dynamic action of food, but does not include energy expended in activity. Normal ranges of REE were found to be ± 10 per cent of predicted REE. Uncomplicated elective operations did not increase REE. Multiple fractures resulted in a 10 to 20 per cent increase for 1 to 3 weeks, while infection produced increases of 15 to 50 per cent. Extensive burn injury resulted in increases from 40 to 100 per cent that lasted for several weeks.

Wilmore et al[85,86] examined whether the increase in $O_2$ consumption seen after burn injury could be the result of increased $O_2$ uptake by the by the burn wound. Twenty-one burn patients were studied between the 7th and 22nd burn day following an overnight fast. Cardiac output and total-body $O_2$ consumption were increased as a function of the severity of the burn. The authors concluded, therefore, that increased whole-body $O_2$ consumption is not a function of increased $O_2$ consumption by the wound, but rather is a generalized systemic response. There is also clearly an increased requirement for glucose by the wound.

## GLUCOSE METABOLISM DURING STRESS

The increase in blood glucose concentration that accompanies injury was first reported in 1877 by Bernard.[12] A study of battle casualties in the 1950s revealed that an injured patient responds to oral glucose loads in a manner similar to that of a diabetic patient.[38] This response, now referred to as the "diabetes of injury," has been noted even when blood glucose concentrations are only minimally elevated. Although insulin levels may be increased, they are low for the prevailing glucose concentration.[28]

The hyperglycemia of injury appears to be a result of increased production relative to normal, because uptake, clearance, and rate of oxidation are all increased.[50] The elevated production rates, however, exceed the increased ability of tissues to clear the glucose. When considered together, the results of these studies suggest that healing tissues require a high plasma concentration of glucose[20] and, because body glucose reserves are limited,[16] lean tissue mass is sacrificed to meet this demand. This breakdown of lean tissue explains the rate of urinary N loss that characterizes the catabolic state.

## FAT METABOLISM DURING STRESSED STARVATION

Because fat serves as the primary energy substrate during stressed and nonstressed starvation, both states are characterized by substantial increases in lipolysis. A hypertonic glucose and AA solution given to a patient who is nutritionally depleted as a result of uncomplicated starvation will suppress endogenous lipolytic activity; as the availability of glucose to meet energy requirements increases, the mobilization of endogenous fat diminishes.[18] Administration of a similar solution to a patient who is metabolically stressed due to injury or infection will also reduce lipolysis, but to a lesser extent than in the nonstressed patient.[19] Thus, in the stressed patient, the mobilization of endogenous fat seems to continue despite the availability of exogenous glucose in quantities sufficient to meet energy needs. Robin et al[70] examined FFA kinetics in stressed patients using C-palmitate turnover. In this study, suppression of FFA oxidation was greater in the unstressed as compared with the stressed fasting subject.

Gluconeogenesis and lipolysis are both increased in fasting in the stressed as well as the nonstressed state. During the fasting unstressed state, compensatory mechanisms result in a shift in fuel sources from gluconeogenesis to lipolysis. A major difference in these metabolic processes is observed when nutrients are infused. During unstressed starvation both processes are significantly reduced, while in the stressed state there is a relative resistance to suppression. Furthermore, endogenous and exogenous oxidation of fat appears to persist even during infusions of hypertonic glucose solution.

These metabolic responses provide the precursors necessary to sustain critical physiologic processes in the absence of food. Glucose is released into the circulation in large quantities to meet the requirements of the CNS and the wound. Fat is released to meet the metabolic needs of skeletal, cardiac, and respiratory muscles. There is resistance to utilization of glucose by these tissues. Metabolic changes develop such that muscle apparently continues to utilize fat even if sufficient glucose is available. Finally, elevated levels of insulin suppress the production of ketone bodies, which, during normal conditions of nutrient deprivation, serve as an alternate energy source.

Over the short term, these mechanisms serve the body well; however, when complications (for example, sepsis) develop and prolong the stress response, the drain on body reserves is so extensive that substrate and energy metabolism will eventually fail to meet organ and whole-body requirements. The result is a reduction in cellular energy levels.[47] Inappropriate substrate administration can exacerbate this phenomenon.[48] In the extreme, this reduction can result in multisystem organ failure.[13] Thus, although the substrate supply may be adequate early in stress, maximal recovery requires the supply of exogenous nutrients.

In catabolic conditions such as injury or sepsis, there are increases in the plasma concentration of a number of proteins that are termed acute-phase reactants; there may be increased rates of synthesis of white blood cells to combat infection and promote wound healing; and there are increased rates of cell proliferation at the wound site. All of these require increased net synthesis of protein that occurs primarily in the liver and bone marrow. The major nondietary source of AAs for this visceral protein synthesis, in the human being, is the breakdown of muscle protein. Major concerns of recent research in this area have been to determine: (1) whether these net changes in muscle protein breakdown and visceral protein synthesis are due to changes in unidirectional protein breakdown, or synthesis, or both together; (2) the nature of the metabolic and endocrine factors mediating these changes; and (3) the effects of nutrition on these processes.[41] Injury seems to be associated with increased protein synthesis and degradation that occur regardless of nutritional state. The mechanisms by which these changes are mediated are unclear.

## MUSCLE AND PLASMA AA PROFILES

It has been shown that muscle is the primary source of N depletion after injury. The cumulative N loss after major elective orthopedic surgery may be 40 to 50 gm.[56] With severe trauma, losses may exceed 100 gm. These losses can be put in perspective by remembering that 1 gm of N is the equivalent of 30 gm of lean tissue. Thus, a loss of 200 gm of N is the equivalent of 6000 gm of lean tissue.

A series of studies by Askanazi and colleagues has been aimed at determining the mechanisms for the N loss that occurs after surgery[4–6] by examining the changes in plasma and muscle AA patterns.

Injury causes characteristic changes from normal values of muscle and plasma AA concentrations. These are seen to varying extents in operative trauma, severe accidental injury, and sepsis. There are two- to threefold increases in muscle concentrations of the large neutral amino acids, including leucine, isoleucine, valine, methionine, phenylalanine, and tyrosine, with much smaller or no changes in plasma concentrations. As a result, muscle–plasma concentration ratios rise as much as threefold. There are increases in net protein breakdown in muscle, and the net extracellular fluid (ECF) compartment will increase. It has been observed that during nutritional repletion, as defined by positive N balance, the expected increases in albumin concentrations are not consistently observed. Serum albumin has long been felt to reflect nutritional status.[59,74] and therefore would be expected to rise when positive N balance develops. The failure of albumin to rise during nutritional repletion suggests to us that the relationship between serum albumin and nutritional status is dependent on factors other than whole-body protein status.[75] This concept is supported by the following observations:

1. Patients with anorexia nervosa are markedly protein-calorie-depleted; however, because this occurs on a balanced nutritional regimen (including protein), there is little expansion of the ECF compartment. Under these conditions serum albumin tends to remain normal.
2. In the healthy adult who is injured or has an acute septic episode, a marked degree of fluid resuscitation is required and is accompanied by a precipitous fall in serum albumin even though whole-body protein is fairly intact. The N balance is negative because this occurs for only a short time; however, there is no significant depletion of N in relation to total-body protein at a time that corresponds to a major decrease in serum albumin levels.

These findings suggest that the relationship between protein synthesis and albumin status is not a direct one, but rather is related to changes in the ECF compartment. When parenteral nutrition is administered, albumin synthesis is increased. However, if expansion of the ECF compartment occurs, the increase in serum albumin mass will not result in increased albumin concentration, but will simply diffuse through an enlarged fluid space, and concentration will not increase. Even if the fractional degradation rate remains constant, because the size of the albumin pool is increased there is an increase in the absolute rate of degradation. As a result, when the ECF compartment is expanded and a concurrent capillary leak syndrome is present, increasing albumin synthesis in response to nutritional support results in an increased whole-body albumin pool and an increased degradation of albumin. With the institution of nutritional support, the albumin pool may increase via a further expansion of the ECF compartment rather than an increase in concentration. When the stress response and capillary leak phenomenon diminish, the ECF compartment contracts. This is associated with a return of serum albumin to normal levels.[75]

Recent studies by Mullen et al[60] indicated that albumin, in addition to its relatively minor role in reflecting nutritional status, is an important predictor of operative mortality and a key parameter of the prognostic nutritional index.[60] This has been confirmed by a series of studies by Starker et al[75] that demonstrated that albumin is important as an indicator of operative mortality; this appears, however, to be due primarily to the extent to which albumin reflects alterations in body–water compartments rather than actual protein status. The initial study by Starker et al used N balance to document the nutritional status of hospitalized patients during nutritional repletion. Measurements of sodium balance were used to indicate alterations in the ECF compartment. By examining concurrent alterations in plasma levels of albumin, body weight, and sodium balance, the relationship of serum albumin concentration to the status of the ECF compartment, rather than to N balance, was established.[59,75] In this study patients were categorized as being either stressed or nonstressed during nutritional repletion. The stressed group consisted mostly of patients with active underlying infection. Figure 1, modified from Starker et al,[75] demonstrates that in the two groups of patients studied (stressed versus nonstressed), there was no significant difference in N balance. Figure 2 demonstrates the changes in sodium balance and serum sodium concentrations. During nutritional depletion, there is a progressively positive sodium balance. It seems that weight loss under hospital conditions does not necessarily reflect the loss of body tissue because an expanded ECF compartment tends to mask the loss of body protein. During nutritional repletion, the nonstressed group showed a negative sodium balance in the first week, whereas sodium balance was markedly positive in the stressed group. Thus, there was a contraction of the ECF compartment during repletion in the nonstressed group. Serum albumin levels, shown in Figure 3, seem to correlate with the alterations in the ECF compartment to a greater degree than with N balance. A rise in serum albumin is observed in the nonstressed group, with a fall during the first 1 to 2 weeks of repletion in the stressed group of patients. The responses observed among the stressed group probably reflect an altered response of the fluid compartments to nutritional repletion. Many of the patients in this group had an underlying infection or other inflammatory processes. It is likely that one of these stresses caused the failure of this group to diurese and normalize the ECF compartment. The expanded ECF compartment presumably diluted the albumin pool, which prevented a rise in serum concentration of albumin.

It should be emphasized that all the patients studied were in positive N

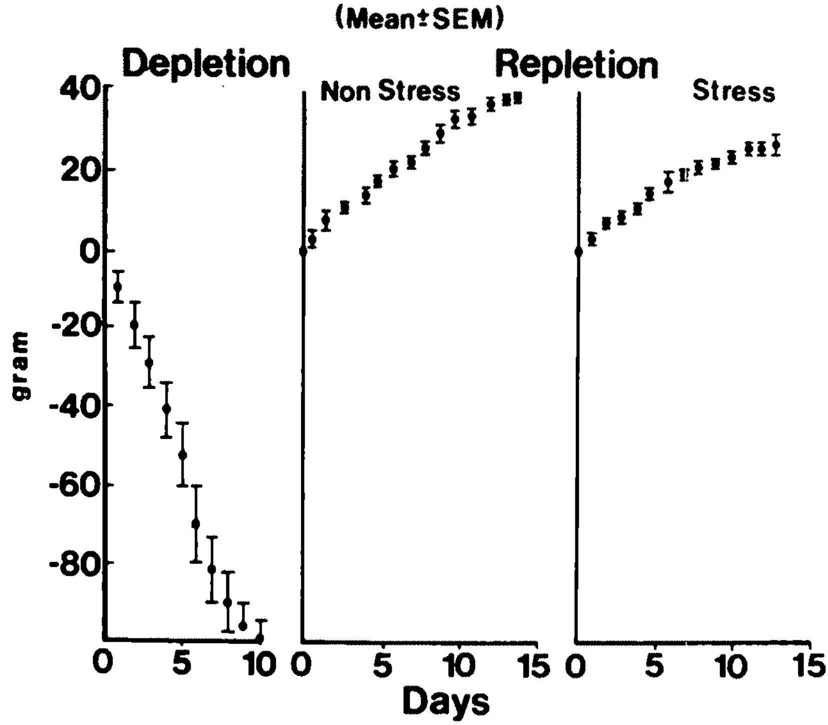

Figure 1. The effects of nutritional support on nitrogen (N) balance in the nonstressed versus the stressed patient are shown. Positive N balance is obtained in both groups. Values are mean ± SEM. (*From* Starker PM, et al: Serum albumin levels as an index of nutritional support. Surgery 91:194–199, 1982; with permission.)

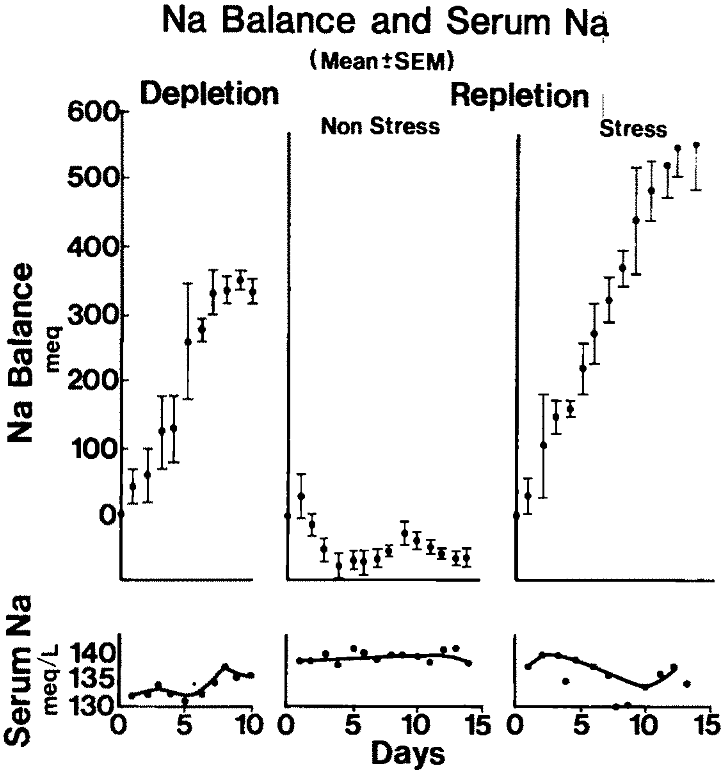

Figure 2. The effect of nutritional support on sodium balance in the nonstressed versus the stressed group of patients is shown. Negative sodium balance developed in the unstressed group, while positive sodium balance developed in the stressed group. Values are mean ± SEM. (*From* Starker PM, et al: Serum albumin levels as an index of nutritional support. Surgery 91:194–199, 1982; with permission.)

balance, and hence were in the anabolic state. Under these conditions, we would have expected albumin synthesis to increase with refeeding.[74] In a study of patients who were in a poor nutritional state postoperatively (as determined by the ratio of exchangeable sodium to exchangeable potassium), Shizgal[72] noted that one patient who developed an intraabdominal abscess had a markedly greater ECF expansion than the other patients, which indicates that nutritional depletion can exacerbate the expansion of the ECF seen in sepsis. Furthermore, ongoing sepsis can prevent normalization of the ECF compartment in response to nutritional support. This may have profound implications for patients, particularly those with respiratory and/or neurologic dysfunction. Larca and Greenbaum[45] demonstrated that patients who received nutritional support and had a rise in plasma protein could be weaned from mechanical ventilation, while those who had a decrease in plasma protein during TPN could not. Bryan-Brown et al[15] reported three anecdotal cases in which cerebral edema that had been unresponsive to conventional therapy improved in response to adequate nutritional support. These studies emphasize the role of nutrition as a factor that will normalize body composition and, by that mechanism, reduce hospital mortality and morbidity. Thus, the endpoint for successful nutritional support would seem to be a normalization of the ECF rather than simply positive N balance for a fixed time period. Preoperative nutritional support should be given until the ECF normalizes, rather than for any arbitrary time period.

In a follow-up study, Starker et al[76] correlated changes in skeletal muscle composition with whole-body electrolyte and N balance in an attempt to establish the contribution made by skeletal muscle to changes in whole-body fluid and electrolyte composition during nutritional repletion. In this study, TPN was administered to 10 patients for up to 25 days. Metabolic rate and whole-body balances of N, sodium, and K were measured daily. Muscle biopsies were taken prior to the administration of TPN, in the middle, and at the end of the nutritional regimen. Prior to the administration of parenteral nutrition, muscle concentrations of water, sodium, and chloride were higher than normal. With the institution of the nutritional support regimen, all three concentrations declined. However, the calculated loss in muscle water could account for only 10 to 20 per cent of the loss in total-body water, and the loss of muscle sodium could account for only approximately one half of the whole-body changes. It would appear, then, that nutritional support results in a restoration of cell mass, with a contraction of the ECF compartment, and although the restoration of cell mass may occur primarily in muscle, the contraction of the ECF compartment must occur in other tissues. We assume that the contraction of the ECF occurs in such important tissues as brain and lung, thereby resulting in the improvements in pulmonary and cerebral status observed during nutritional-support regimens.

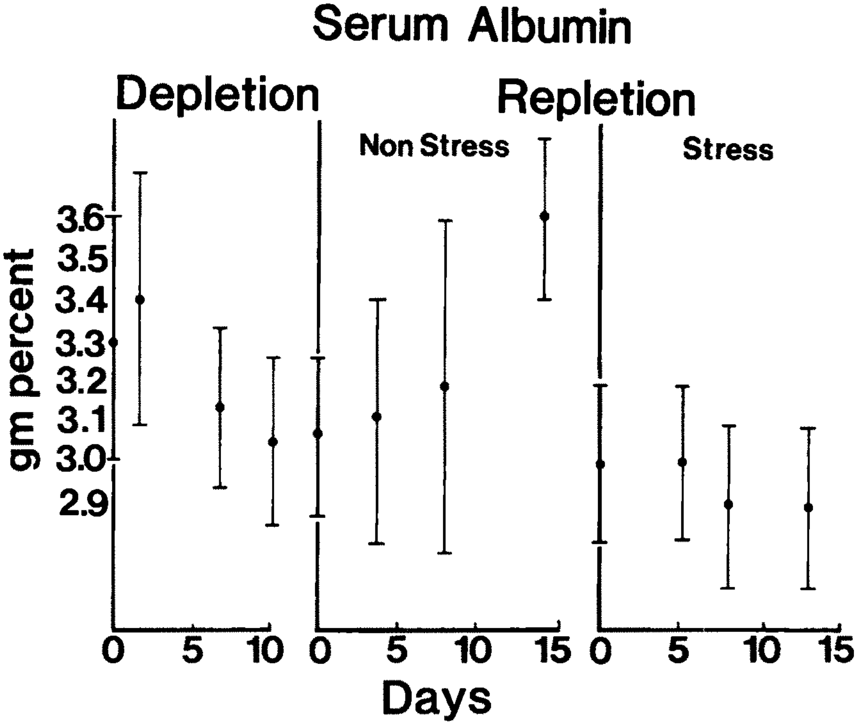

Figure 3. The effect of nutritional support on serum albumin level in the nonstressed versus the stressed group of patients is shown. (*From* Starker PM, et al: Serum albumin levels as an index of nutritional support. Surgery 91:194–199, 1982; with permission.)

For patients requiring parenteral nutrition prior to reoperation, it is quite clear that expansion of the ECF compartment represents a serious risk factor. In a prospective study,[77] postoperative course was correlated with the preoperative response to nutritional support. Thirty-two patients with nutritional depletion received an average of 1 week of TPN prior to major abdominal reoperation. Of the 16 patients (Group I) who exhibited the characteristic response to early nutritional support-diuresis of the expanded ECF compartment with a resultant loss of weight (127.9 ± 5.7 lb to 124.6 ± 5.8 SEM lb, $P < 0.001$) and rise in serum albumin (3.21 ± 0.14 gm per dl to 3.46 ± 0.15 gm per dl, $P < 0.001$), only one developed a complication in the postoperative period. The other 16 patients (Group II) did not exhibit this response. They retained additional fluid, gained weight (119.3 ± 8.1 lb to 121.3 ± 8.2 lb, $P < 0.025$), and showed a decrease in serum albumin levels (3.14 ± 0.14 gm per dl to 3.00 ± 0.14 gm per dl, $P < 0.01$). Eight of these patients developed a total of 15 postoperative complications ($P < 0.01$). In a follow-up study, these investigators[78] demonstrated that in patients (Group III) who did not have a diuresis after 1 week of TPN, a reduction in morbidity and mortality would occur with 6 weeks of preoperative TPN (Tables 1 and 2).

## NUTRITIONAL SUPPORT IN THE POSTOPERATIVE PERIOD

In a teleologic sense, the response to injury and infection can be viewed as a mobilization of body protein, fat, and carbohydrate stores to ensure normal or above-normal circulating levels of substrate (glucose, FFAs, and AAs) in the absence of dietary intake (Tables 3 and 4). The persistance of gluconeogenesis, despite high serum concentrations of glucose, reflects the urgent nature of the requirement for glucose. Fat is mobilized to meet the energy needs of cardiac and skeletal muscle so that glucose may be spared for the tissues that specifically require it, such as the CNS and the cellular immune system. This pattern, unlike that observed in fasting normal human beings, does not readily yield to nutritional manipulation. Consequently, hypertonic glucose dosages are usually ineffective in these

**Table 1.** *Changes in Nutritional Status During Preoperative TPN**

| | GROUP I† | GROUP II† | GROUP III |
|---|---|---|---|
| Number of patients | 23 | 20 | 16 |
| Body weight (lb) | 126 ± 5.2 | 118.2 ± 6.4 | 117.6 ± 5.2 |
| Pre/post 1 week TPN | 123.2 ± 5.2§ | 120.1 ± 6.4‡ | 119.8 ± 5.4§ |
| | | | (121.9 ± 5.8) |
| Serum albumin (gm per dL) | 3.19 ± 0.10 | 3.14 ± 0.12 | 3.11 ± 0.16 |
| Pre/post 1 week TPN | 3.44 ± 0.11§ | 3.00 ± 0.13‡ | 2.90 ± 0.16‡ |
| | | | (3.27 ± 0.10) |
| Days preoperative TPN | 7.3 ± 0.8 | 6.8 ± 0.8 | 33.4 ± 3.2 |
| Operating room time (hr) | 3.6 ± 0.4 | 4.4 ± 0.7 | 3.0 ± 0.4 |

TPN, total parenteral nutrition. *Numbers in parentheses represent the values prior to operation following the entire period of nutritional support.

†Sixteen patients in each group previously reported.[77]

Comparing pre-TPN values with those obtained 1 week post-TPN: ‡$P < 0.01$; §$P < 0.001$. Comparing values after 1 week of TPN with those obtained after 3–6 weeks TPN: $P < 0.01$.

patients; more importantly, they can pose an additional stress by precipitating increases in oxygen consumption, carbon dioxide production, and norepinephrine excretion, and by inducing hepatic complications. These findings should not be interpreted to indicate that glucose infusion is contraindicated in stressed patients; on the contrary, a certain level of carbohydrate intake is essential to meet obligatory glucose requirements. The importance of glucose has been underscored by data associating the administration of AAs alone with a reduction in cellular energy levels in injured patients.[25] It seems that a nutritional regimen appropriate for a patient under metabolic stress would consist of a relatively modest concentration of glucose administered with AAs and other essential nutrients.

Although fat emulsions represent the logical alternative to glucose loading in patients with exaggerated caloric requirements and a diminished ability to clear exogenous glucose, there is some disagreement concerning the use of these products as an energy substrate. In the United States, fat emulsions are prescribed primarily for the prevention of essential fatty acid deficiency.

The N-sparing effects of fat emulsions as compared with those of glucose solutions have been studied extensively. At low dosages, carbohydrate is clearly superior to fat in this capacity, but when carbohydrate is administered in dosages higher than 600 kcal per day, the N-sparing abilities of fat and carbohydrate are essentially equal.[61] Long et al[51] performed studies in five severely burned patients to examine the effects of four glucose dosages and three fat dosages on N retention. Their findings indicated that glucose administration significantly improved N balance while fat administration did not. However, it should be noted that the evaluated dosages equaled, but did not exceed, the minimum requirement for glucose. Furthermore, the investigators did not attempt to determine whether replacing a portion of glucose calories with fat calories would maintain the N-sparing effect and

**Table 2.** *Postoperative Complications*

| COMPLICATIONS | GROUP I | GROUP II | GROUP III |
|---|---|---|---|
| Mechanical | | | |
| Prolonged ventilatory support | 0 | 4 | 0 |
| Fistula | 0 | 0 | 1 |
| Wound dehiscence | 0 | 1 | 0 |
| Anastomotic leak | 0 | 1 | 0 |
| Total | 0 | 6 | 1 |
| Infections | | | |
| Sepsis | 0 | 2 | 0 |
| Pneumonia | 1 | 3 | 0 |
| Wound infection | 0 | 3 | 1 |
| Abscess | 0 | 1 | 0 |
| Total | 1 | 9 | 1 |
| Death (nutritionally related) | 0 | 2 | 0 |
| Total Complications | 1 | 17 | 2 |
| Total number of patients developing complications | 1* | 9 | 2† |
| Per cent of patients developing complications | 4.3 | 45 | 12.5 |

*$P < 0.01$ (Group I/Group II).
†$P < 0.05$ (Group II/Group III).

**Table 3.** *Stressed versus Unstressed Starvation—Summary*

| | FASTING | TRAUMA/SEPSIS |
|---|---|---|
| Metabolic rate | Low | High |
| RQ – 5% Dextrose | Low (0.7) | Low (0.7) |
| Hypercaloric glucose | Rises to 1.0 and higher | Remains low; below 1.0 |
| Nitrogen balance | Negative, but improves over time with continued fast; becomes positive rapidly with refeeding | Markedly negative, no compensation with time; will improve but does so slowly with refeeding |
| Serum glucose | Low | High |
| Lipolysis | Elevated, but easily suppressed with glucose administration | Markedly elevated; poorly suppressed with glucose administration |
| Gluconeogenesis | Initially elevated, but decreased with time; easily suppressed with glucose administration | Markedly elevated; poorly suppressed with glucose administration |

RQ = respiratory quotient; N = nitrogen.

minimize the incidence of complications associated with hypertonic glucose infusions. Because results of an earlier study suggested that using fat to supply part of the nonprotein caloric load did not diminish N balance, this consideration warranted further investigation.[51]

To this end, Nordenstrom et al[63] designed a study to compare the effects of what is now known as the "glucose system" of TPN (all nonprotein calories supplied in the form of glucose) with those of the "lipid system" of TPN (equal portions of the nonprotein caloric load supplied as glucose and fat). All patients received the same N dosage. Although no discernible differences were detected in the N balances achieved with the two regimens, the "lipid system" was associated with a lesser calorigenic response and decreased norepinephrine excretion.[62] Results of another study conducted by this group indicated that there was a reduction in carbon dioxide production

**Table 4.** *Early Versus Late Sepsis—Summary*

| | EARLY SEPSIS | LATE SEPSIS |
|---|---|---|
| Metabolic rate | High | Low |
| Respiratory quotient | Low | High |
| Fat clearance | Increased | Decreased |
| Nitrogen balance | Negative | Markedly negative |
| Serum glucose | High | Very high |

*Adapted from* Giovanni I, Boldrini G, Castagneto M, et al: Respiratory quotient and patterns of substrate utilization in human sepsis and trauma. JPEN 7:226, 1983.

in patients receiving the lipid system.[8] It seems likely, therefore, that a regimen supplying nonprotein calories in the form of both glucose and fat may be particularly appropriate for the stressed patient with respiratory compromise.

## LATE STRESS—MULTISYSTEM ORGAN FAILURE

The fuel patterns discussed in the preceding sections pertain to the flow phase of stress, which begins 24 to 48 hours after injury. As we learn more about stress metabolism, it is becoming increasingly clear that these patterns reverse in the latter stages of sepsis.[35,49] Advanced-state sepsis is characterized by reduced fat and glucose utilization and diminished tissue concentrations of high-energy phosphates. As these effects become more pronounced, nutritional support becomes progressively less effective. Lindholm and Rossner[49] determined that lipid clearance, in particular, is drastically impaired in the final stages of critical illness (Figure 4). In a study of the metabolic and cardiorespiratory patterns of patients under severe metabolic stress, Giovanni et al[35] found that the respiratory quotient (RQ) at any given glucose dosage was low by comparison with that recorded for nonstressed patients given equivalent glucose infusions. In a separate study, patients with advanced sepsis and massive N loss showed decreases in metabolic rate attended by unexpected rises in the RQ.

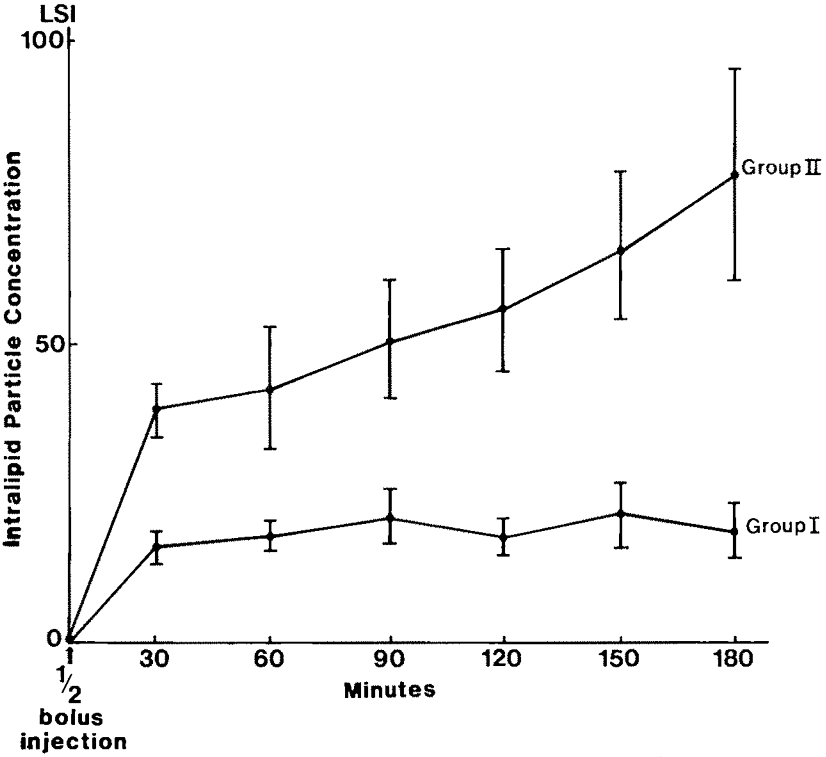

Figure 4. Lipid clearance in critical illness. (*From* Lindholm M, et al: Rate of elimination of the intralipid fat emulsion from the circulation in ICU patients. Crit Care Med 10:740–746, 1982; with permission.)

## NEW HORIZONS OF NUTRITION SUPPORT

### Effects of Intravenous Fat Emulsions and Prostaglandins on the Lung

***Experimental studies.*** Prostaglandins (PGs) have received the attention of pulmonary researchers because of their mediator effects within the lungs. These include contractile effects on bronchial smooth muscle and variable actions on the pulmonary circulation. Studies in different species have demonstrated that a decrease in pulmonary vascular substances increases the vascular and bronchial resistance. These effects for IVFE and arachidonic acid are blocked after administration of indomethacin (a cyclooxygenase inhibitor), suggesting that the effects are due to conversion into PGs in the cyclooxygenase pathway. The PGEs and $PGI_2$ (prostacyclin) are pulmonary vasodilators, whereas other PGs such as $PGF_2$ have vasoconstrictive effects, as do most of the thromboxanes and leukotrienes. A bolus dose seems to provoke a vasoconstrictive response, while a slow infusion produces a vasodilatory response. This suggests that slow infusions of fat result in a relative predominance of vasodilating (PGE) substances, while rapid infusion overwhelms this pathway and leads to a predominance of vasoconstrictive PGs. The vasodilating effect of the PGEs and $PGI_2$ have been utilized clinically to treat pulmonary hypertension, as well as to improve blood flow for peripheral vascular disease, for unstable angina after myocardial infarction, and for maintaining patency of the ductus arteriosus in newborns.

Previous studies have generally attributed the IVFE-related alterations in lung function to increased TG levels. However, more recent experimental studies in animals have not shown any relation between TG increases and lung function. These studies have documented an increase in PG plasma levels during IVFE infusion; the PG alterations appear to cause the changes in lung function. Inwood and colleagues[39] found no ventilatory changes in rabbits with normal lung function receiving IVFE. In rabbits with lung damage after pretreatment with oleic acid, they found an IVFE-related decrease in $PaO_2$ and increase in the alveolar–arterial difference in oxygen tension, both of which returned to baseline without TG normalization. Indomethacin prevented the changes in lung function despite the TG increase.

These studies support the hypothesis that the IVFE-related changes in lung function are in fact PG mediated. The effects can best be explained by changes in the distribution of intrapulmonary blood flow consequent to PG-mediated alterations in pulmonary vasomotor tone.[37] The changes in blood flow lead to an increase in ventilation/perfusion (V/Q) inequalities, which can explain the $PaO_2$ and $P(A\text{-}a)O_2$ changes related to IVFE. In the lung-damaged groups, there was a lower baseline $PaO_2$ caused by secondary hypoxic vasoconstriction; with vasodilators such as $PGE_2$ and $PGI_2$, the perfusion of poorly ventilated alveoli should increase. This in turn would increase the intrapulmonary right to left shunt and cause a further decrease in $PaO_2$. The same mechanism for hypoxia has been observed in other situations where vasodilators have been given to patients with impaired lung function and V/Q imbalance.[68,84] In the normal lung groups with no baseline hypoxic vasoconstriction, the experimental studies showed no IVFE-associated $PaO_2$ decrease.

***Effects of dose, rate, duration, and fatty acid content of IVFE infusion.*** Infusion of IVFE and arachidonic acid has a mixed action on the pulmonary vascular bed. When given as a bolus or rapid infusion, a vasoconstrictive response is reported; when IVFE is given as a slow infusion, a vasodilating effect is seen. The reason for these results in unclear, but it has been suggested that an alteration in PG production is a factor because the vasomotor response is blocked by indomethacin.[36,37,39,55] During a slow infusion it is likely that there is a net increase in vasodilating and anti-inflammatory PGs like $PGE_2$ and $PGI_2$. During a bolus or a rapid infusion, however, the excessive amount of substrate may overwhelm the enzymatic pathways for $PGI_2$ and $PGE_2$ metabolism, resulting in an increased production of potent vasoconstrictives such as thromboxane $TxA_2$. In general, the anti-inflammatory PGs have a vasodilatory effect on the pulmonary vascular bed, in contrast to the vasoconstrictive effects of the proinflammatory thromboxanes.[43,46,81] We have therefore suggested that the IVFEs exert an anti-inflammatory response when given as a slow infusion and may have a proinflammatory response when given as a bolus or rapid infusion.[10,73] We have observed in cystic fibrosis (CF) patients that patients who receive IVFE report progressive thinning of secretions up to a point with increasing doses of Intralipid. Above a certain level of the rate of lipid infusion, however, the secretions got thicker; this may be due to the result of thromboxane production as linoleic acid saturates in PGE system.

In addition to the rate of infusion, the IVFE effects appear to be dependent on the duration of the infusion. Because the PGs formed locally in the lung in response to lipid infusion are not stored, the effects are not likely to be sustained after the cessation of the infusion. In experimental lung models, pulmonary vasomotor tone returned to baseline values 45 to 120 minutes after the IVFE infusion.[36,55] To achieve IVFE-related effects on inflammation, the duration of infusion seems, therefore, to be important. In the previously mentioned reports on IVFE infusion in CF patients,[24,26,27,44,71] the fat infusion was given over 2 to 4 hours in intervals varying from 2 to 6 weeks. This rate of infusion may be too rapid to allow the anti-inflammatory response to develop, thus explaining the variable results. When fat has been given more aggressively as part of TPN to CF patients, the overall results have been more promising. We gave a lipid-based TPN regimen daily over 12 hours for more than 4 months and have suggested that the reported anti-inflammatory pulmonary response was due to the fact that the IVFE was given often and over a lengthy period of infusion.

The content of polyunsaturated fatty acid in the IVFE may also be important in determining the effect on PG synthesis. Intralipid and Liposyn contain 54 per cent and 77 per cent, respectively, of linoleic acid, which is the precursor of the n-6 family of polyunsaturated fatty acids (PUFA). Intralipid has 8 per cent and Liposyn almost no linolenic acid, the precursor of the n-3 family of PUFA (Liposyn II represents a mixture of the two). Several epidemiologic, clinical, and experimental studies[21,42,69,82] have reported a dampening of inflammation when the n-3 fatty acids are enriched relative to the n-6 family in the diet. This is explained in part by production of the "3" series of PGs from eicosopentanoic acid (EPA), which seem to have a net anti-inflammatory response. EPA also reduces the production of $TxA_2$ from arachidonic acid via competition for the cyclooxygenase pathway. By modulating the content of PUFA in the IVFE it may be possible to influence the effect of the IVFE on inflammation and other PG-mediated effects on vasomotor tone and platelet aggregation in the lung.

## Amino Acids and Ventilation

It has been shown that ventilatory drive is enhanced by progressively increasing levels of N intake. Increasing N intake will lead to enhanced protein synthesis and a more rapid restoration of lean body tissue. On occasion, dyspnea has been observed during the administration of $CO_2$ in patients who are receiving high-protein intakes, accompanied by increased levels of ventilation, and normal or low $PaCO_2$ values. Patients with dyspnea have been shown to have increased neuromuscular drive, although the ability of the lung–thorax system to increase $V_E$ is limited.

Previous studies from this laboratory have demonstrated that the respiratory drive and metabolic rate decreased during 1 week of semistarvation with 5 per cent dextrose and that an amino acid infusion similar to the infusion of the standard solution in this study increased oxygen consumption, minute ventilation, and mean inspiratory flow rate after 4 hours of infusion.[83] Restoration of normal levels of gas exchange and ventilation was observed after infusing the standard amino acid solution for 24 hours. TPN has also been observed to increase the ventilatory demand, presumably via increased carbon dioxide production due to the large carbohydrate loads.[7] Increasing the amino acid content of TPN increases the ventilatory demand by increasing both oxygen consumption and ventilatory drive.[9] This study shows that not only the quantity of amino acids but also the composition of the amino acid solution affects the ventilatory response. The accentuation of the respiratory effects of amino acids by branched chain amino acids may have important clinical relevance. Work of breathing and respiratory drive are often increased in patients with chronic obstructive pulmonary disease, in postoperative patients requiring mechanical ventilation, and in patients with respiratory failure.[11,30,87] Increasing respiratory drive will further increase the work of breathing and make fatigue of respiratory muscles more

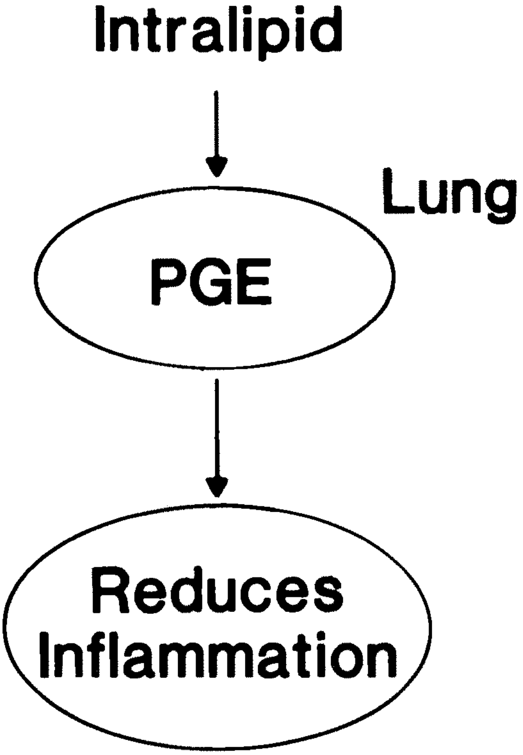

Figure 5. The anti-inflammatory effect of intralipid is schematically depicted.

likely to ensue.[58] Hence, restricting the supply of branched chain amino acids in these conditions may prove beneficial. On the other hand, recovery of normal ventilatory responsiveness may be enhanced in patients with decreased ventilatory drive due to malnutrition or prolonged administration of 5 per cent dextrose. The difference between the ventilatory responses to the two amino acid solutions is unlikely to be of clinical significance in patients with normal ventilatory reserves. However, the increase in ventilatory demand due to parenteral nutrition seems to be magnified in critically ill patients.[9,30] Hence, benefits from the presumed "anticatabolic" effects of branched chain amino acid administration should be weighed against the possible increase in ventilatory demand.

In a study by Takala et al,[79] two amino acid solutions, one enriched with branched chain amino acids, were infused at rates corresponding to those in routine clinical use. The effects of both amino acid solutions on respiration and oxygen consumption were observed after 4 hours of the infusion. The branch chain amino acid-enriched solution appeared to magnify the respiratory stimulation observed following the infusion of standard amino acid solutions. The increase in minute ventilation and mean inspiratory flow rate and the decrease in resting arterial carbon dioxide tension, in conjunction with unchanged carbon dioxide production, are indicative of increased central respiratory drive.[57] The augmented responsiveness to arterial carbon dioxide tension during the carbon dioxide-response study, as demonstrated by the shift to the left of the minute ventilation–arterial carbon dioxide tension relationship, indicated an additive increase in the ventilatory response to carbon dioxide.[57] The increase in metabolic rate that occurred following the amino acid infusions may explain the increased minute ventilation and mean inspiratory flow rate during the infusion of the standard amino acid solution, but it cannot fully account for the augmentation of resting ventilation and the ventilatory response to carbon dioxide during the infusion of the branched chain amino acid-enriched solution because the changes in oxygen consumption were similar between the two solutions. Arterial carbon dioxide tension decreased during the branched chain amino acid infusion but not during the standard amino acid solution, despite similar changes in carbon dioxide production and minute ventilation.

Serotonin and its precursors depress both resting ventilation and the ventilatory responses to carbon dioxide in experimental animals, evidently via serotoninergic activation in the brain.[3,52] In experimental animals the brain serotonin content is related to the brain content of its precursor, tryptophan,[32] and tryptophan competes with the other large neutral amino acids of the same transport system into the brain.[34] If the same is true for human beings, an increase in the plasma ratio of the large neutral amino acids to tryptophan may well contribute to increasing respiratory drive during the high supply of branched chain amino acids.

## NUTRIENT INFUSION AFFECTS DRUG METABOLISM

A study by Pantuck et al[67] demonstrated that the caloric source of intravenous nutritional regimens can influence oxidative drug metabolism in human beings. Antipyrine metabolism increased, as evidenced by a decrease in $t^{1/2}$, a decrease in area under the curve (AUC), and an increase in metabolic clearance rate (MCR) for this drug in four subjects when they were switched from an intravenous nutritional regimen consisting of 5 per cent dextrose to an essentially isocaloric intravenous nutritional regimen consisting of amino acids as Aminosyn 3.5 per cent. While the increase in antipyrine metabolism was small in some subjects, it was of considerable magnitude in others.

Amino acids and dextrose in equal caloric amounts are not equivalent sources of energy and, in addition to being caloric sources, have multiple, complex, and in many ways, different effects on physiologic processes and body composition. The mechanism by which intravenous dextrose and intravenous amino acids differentially affect antipyrine metabolism is not known. Clinicians should be aware that the caloric source in intravenous nutritional regimens can affect oxidative drug metabolism. A change in metabolism of the magnitude of the change in antipyrine metabolism seen in some of our subjects when they were switched from intravenous dextrose, 440 kcal per day, to intravenous Aminosyn, 480 kcal per day, for only 1 day would significantly alter the therapeutic effect of toxicity of many drugs. It is possible that the intravenous administration of amino acids for a longer time may result in an even greater change in drug metabolism. Additional studies are needed to determine the effects of commonly used intravenous nutritional regimens on the metabolism of therapeutically important pharmacologic agents. Studies are also needed to elucidate the mechanism(s) by which intravenous nutrients influence oxidative drug metabolism.

## SUMMARY

Administration of preoperative TPN must be geared to the needs and reactions of the individual patient. While some patients will respond to refeeding (parenteral or oral) within a week, others (particularly stressed patients) may require as much as 6 weeks of nutritional therapy before elective surgery. A key predictive factor in determining a given patient's response to preoperative TPN appears to be the serum albumin level, as an indicator of ECF status.

We now know that there are specific patients for whom the side effects of excessive glucose infusion may offset the physiologic benefits of TPN. This category consists of patients who are under significant metabolic stress as a result of injury or infection. For these people, delivery of the maximum glucose dosage possible may not be an acceptable therapeutic goal. In such circumstances it is essential to recognize the cost at which lean body mass is being preserved. Recent findings indicate that during the metabolic stress, matching glucose dosage to glucose need may be preferable to supplying an overabundance of glucose. Fat emulsions, previously prescribed solely for their ability to prevent essential fatty acid deficiency, have gained acceptance as auxiliary caloric substrates and may provide the answer to satisfying increased energy requirements in the presence of impaired glucose utilization. As usage of these products increases, some of the metabolic complications associated with glucose loading may be avoided.

While there is clearly a need for some glucose during stress, the question of whether to supply the balance of required nonprotein calories as glucose of fat remains to be answered. What is certain is that prevention of essential fatty acid deficiency necessitates the administration of at least 5 per cent of the total energy requirement in the form of fat. Although we usually supply at least half of the nonprotein caloric load as fat, the composition of the TPN regimen is ultimately governed by the patient's clinical condition and responses to nutritional support.

Putting the discussion of caloric substrate aside, we arrive at the issue that is probably most crucial to the success of nutritional support—that of timing. It is clear that nutritional support in any form becomes progressively less effective as the severity of the stress response increases. Consequently, if such supportive therapy is to benefit the patient, it must be instituted early in the course of illness. If a patient has been previously well nourished, the goal should be prevention of major protein losses while complications are minimized. Under these conditions, nutritional support may be given via peripheral vein, as a combination of nutrients that approximates metabolic expenditure. If the stress is expected to continue for longer than 5 to 7 days, a full central venous support regimen should be instituted that aims for, as a minimum, N equilibrium. In the nutritionally depleted patient, an attempt to achieve positive N balance should be made as early as is practical.

New horizons in metabolic support are extremely exciting and will make use of the pharmacologic effects of nutritional support to modify fundamental physiologic processes.

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# Septic Shock

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Septic shock is a clinical syndrome produced by microorganisms, their toxins, or both, invading the blood stream of a host. Traditionally, gram-negative bacteria have been associated with septic shock, however, a wide variety of microorganisms including gram-positive bacteria, fungi, protozoa, and viruses have been implicated in initiating this syndrome.[7,16,48] The hallmark of this disease is septicemia with cardiovascular instability, evidenced by systemic hypotension. This syndrome, however, is remarkably complex. An array of exogenous toxins and endogenous mediators may lead to progressive multisystem organ failure during a period of hours to days, through mechanisms that are still poorly understood.[41,42,49,50]

Septic shock, the most common cause of death in intensive care units, is largely a nosocomial problem. The increase in the incidence of sepsis has been created in part by advances in medical technology.[41,49–51] Paradoxically, septic shock has become more prevalent with the widespread use of potent antibiotics, which disrupt the normal flora, predisposing the host to colonization by more resistant organisms.[20,46] Septic shock, however, has not attracted the attention of the public like the acquired immunodeficiency syndrome, cancer, or heart disease, because it is a hidden problem. Septic shock often occurs as a complication of other medical problems, thereby contributing to the mortality of a variety of different conditions and illnesses. Thus, patients with septic shock are divided among many of the different hospital services; medicine, gynecology, pediatrics, anesthesiology, and surgery.[28,42] Because of this and the lack of a centralized reporting system, it is difficult to estimate the true incidence and mortality of this disease. Current studies of gram-negative sepsis estimate that there are between 100,000 and more than 300,000 cases each year with a 40 per cent to 50 per cent incidence of shock. If shock does develop, the reported mortality is 40 per cent to 90 per cent.[31,42,46] Further, one must add to these estimates for gram-negative septic shock a growing contribution from other microorganisms including gram-positive bacteria and fungi to appreciate the true impact of this disorder on medical practice.

In the future, increased use and further development of chemotherapy, immunotherapy, invasive procedures, surgery, and life support systems,

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will continue to promote an increasing incidence of this highly lethal complication.[20,42]

## CLINICAL MANIFESTATIONS OF SEPTIC SHOCK

The natural history of septic shock has probably been altered by present-day therapy (antibiotics, fluids, pressors, etc.), and the human disease can only be described in this context. The initial presentation of septic shock is usually tachycardia and hypotension with altered temperature regulation, most commonly hyperthermia and occasionally hypothermia. This cardiovascular instability may last from hours to days, but with therapy, commonly resolves during a 24- to 96-hour period in the patients who survive the acute phase of the illness.[38-42,48] During this early phase of cardiovascular instability, the symptoms on physical examination can vary from cold cyanotic skin to warm skin with bounding pulses. These findings are governed by alterations in the regulation of blood flow and the degree of vasoconstriction. Every organ system is affected during this period of altered blood flow regulation, and in a subgroup of patients signs of progressive organ dysfunction may begin to manifest during this stage of the syndrome.

Tachypnea with or without hypoxia, oliguria, icterus, and mental confusion may represent ominous findings in the septic patient, and such findings may portend the development of organ failure. Aggressive intervention at this point may interrupt this progressive cycle of tissue injury, but despite flawless medical care and prompt cardiovascular sterilization, multisystem organ failure may still relentlessly develop. Careful evaluation of the patient at this stage, however, may reveal evidence of an abscess, suggest an etiologic agent (that is, green pus with the odor of grapes characteristic of *Pseudomonas aeruginosa*), or even provide a specific diagnosis (that is, the erythematous rash associated with toxic shock syndrome), thereby guiding therapy and improving the chances of successful management.

## PATHOPHYSIOLOGY

The pathophysiology of septic shock is incompletely understood. A popular belief is that a combination of direct effects of microbial agents, microbiologic toxins, and activation of endogenous (potentially harmful) mediators results in the cardiovascular instability and multisystem organ failure (Fig. 1) of septic shock.[42]

Normally, host defense systems keep bacteria and other microorganisms from developing a site of infection in the body. A nidus of infection may develop due to a breakdown in defense systems (that is, loss of skin and/or mucous membrane integrity, dysfunction of tracheobronchial cilia, loss of white blood cells, absence of certain complement components, etc.) or through increased virulence of the microorganism. If the microorganism overwhelms the host, there is an invasion of tissues and release of microorganisms and their toxins into the blood stream. This results in contact within the vascular space, between the foreign proteins and toxins of the microorganism and the cellular (that is, macrophages, basophils, eosinophils, lymphocytes, mast cells, neutrophils) and humoral defense systems (that is, complement and immunoglobulins). This leads to the activation and release

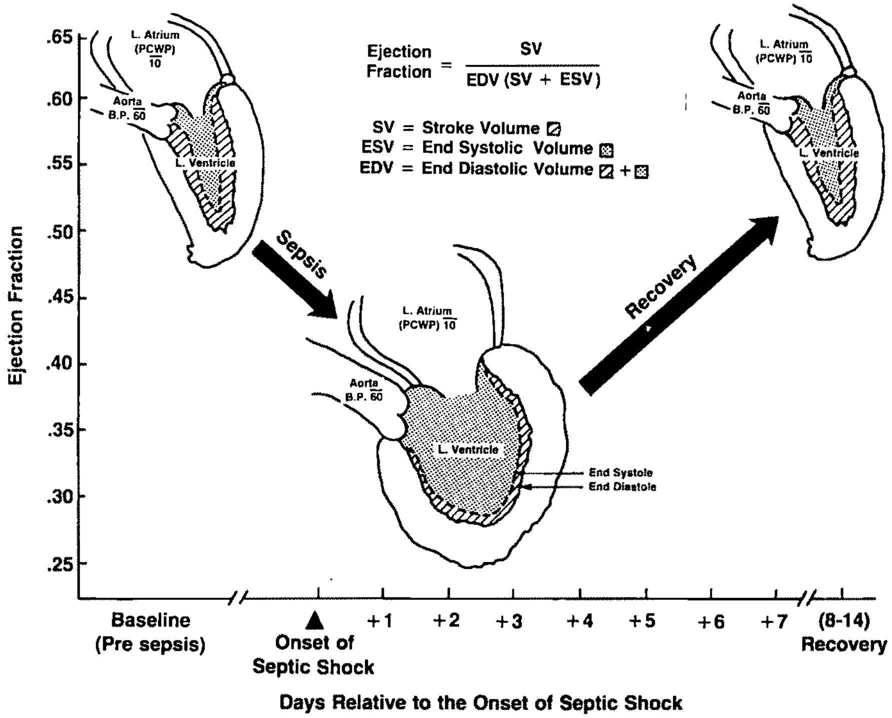

Figure 1. A schematic diagram depicting the serial changes in left ventricular size and function during the first 14 days after a bout of septic shock in a canine model that simulates the human disease.

of immune mediators with potent vascular effects that promote cardiovascular instability. In addition, various potential endogenous toxins (superoxide, endorphins,[24] tumor necrosis factor,[3,4,8,9] arachidonic acid metabolites,[2,21,22] complement,[11,12,18] Hageman factor,[10,30] histamine, kinins,[30,45] myocardial depressant factor,[41] interleukin-1[2]) and bacterial toxins may directly damage the vascular endothelium and lead to loss of vascular integrity and edema. This loss of vascular integrity and subsequent capillary "leakiness" are thought to be the main factor in producing the noncardiogenic pulmonary edema of sepsis-induced respiratory failure.[1,5,26] In other organs, endothelial cell damage may further worsen microcirculatory abnormalities and through capillary disruption may contribute to additional tissue injury. There is evidence, for instance, that damage of the peritubular capillaries is involved in the development of acute tubular necrosis and renal failure in septic shock. This cascade of mediator release and small vessel injury, once set in motion, ultimately may lead to the death of the host.[42,50]

## SPECIFIC ORGAN DYSFUNCTION

### Cardiovascular System

During the last 8 years at the National Institutes of Health, we have studied the cardiovascular effects of septic shock in humans and animals. The first part of this section will present data from human studies done in our intensive care unit, followed by a series from a canine model of septic shock that we have developed.

***Human Studies.*** As stated, the most common initial cardiovascular presentation of this disease is hypotension and tachycardia. The hypotension of septic shock may be so severe as to be unresponsive to fluids or pressor therapy. As opposed to other forms of shock (for example, cardiac, hypovolemic, obstructive) in which the cardiac ouput is substantially reduced, the cardiac ouput in septic shock with adequate intravascular volume is usually not depressed, but normal or increased.[40] Myocardial function (Fig. 1), however, is affected as evidenced by profound decreases in left and right ventricular ejection fraction.[17,38–40]

The reason for this maintenance of cardiac output, despite evidence of myocardial depression may relate to a septic shock induced change in cardiac diastolic function. During septic shock, the heart dilates and thus via a Frank-Starling mechanism, may maintain stroke volume and cardiac output.[27,32–42] In summary, the most common cardiovascular profile during septic shock is hypotension, tachycardia, a dilated left ventricle, a depressed left ventricular ejection fraction, and a normal or high stroke volume and cardiac output. In survivors, these changes return to normal over 7 to 10 days.

A common cause of death from septic shock in intensive care units is multiple organ system failure (Fig. 2), however, the vascular and cardiac defect may also directly affect lethality by resulting in irreversible hypotension. This hypotension of septic shock can occur despite a high cardiac output and can progress in the face of treatment with large quantities of intravascular volume to normalize intracardiac pressures and high concentrations of catecholamines. Death during septic shock also may be related to direct myocardial depression so severe as to overcome compensatory cardiac mechanisms and lead to a low cardiac output, severe heart failure, and death. Depending on a person's left ventricular function, these two septic shock induced defects in the cardiac and vascular systems may play varying roles in a patient's demise. In general, approximately 50 per cent of nonsurvivors die with multiple organ system failure, 40 per cent die of a severe decrease in systemic vascular resistance, and 10 per cent die of progressive hypotension due to a decrease in cardiac performance.[37–39,42,50]

The etiology of these cardiovascular defects is unknown. Human studies at the National Institutes of Health have demonstrated that coronary blood flow is normal or elevated.[13] However, a circulating factor has been demonstrated during the myocardial depression in septic shock that depresses in vitro myocardial cell performance.[41] In a recent study, 20 patients admitted to the medical intensive care unit with septic shock had simultaneous serial blood samples and cardiac function using simultaneous thermodilution outputs and radionuclide heart scans. Myocardial cells from newborn rats were grown in tissue culture. The heart cells beat spontaneously and a single cell's contraction could be quantitated. Serum obtained from patients with septic shock and a decreased radionuclide-determined left ventricular ejection fraction could frequently depress the beating rat heart cells. This study demonstrated clear evidence of a myocardial depressant substance during human septic shock that was not found in control serum. In survivors of septic shock, repeat heart scans after 7 to 10 days showed that cardiac performance returned to normal and serum assays for myocardial depressant activity were not longer present.[41] Preliminary isolation of this molecule suggests that its molecular weight is about 10,000 Daltons. Further studies are needed to clarify fully the mechanism of this cardiovascular defect and its molecular mechanism factor.

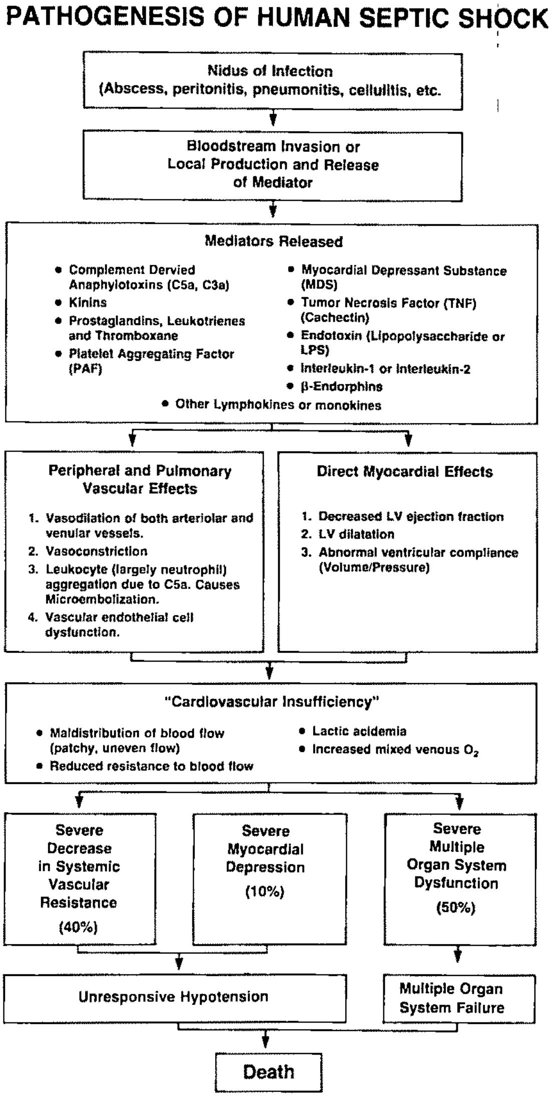
PATHOGENESIS OF HUMAN SEPTIC SHOCK
Nidus of Infection
(Abscess, peritonitis, pneumonitis, cellulitis, etc.
Bloodstream Invasion or
Local Production and Release
of Mediator
Mediators Released
• Complement Dervied Anaphylotoxins (C5a, C3a)
• Kinins
• Prostaglandins, Leukotrienes and Thromboxane
• Platelet Aggregating Factor (PAF)
• Myocardial Depressant Substance (MDS)
• Tumor Necrosis Factor (TNF) (Cachectin)
• Endotoxin (Lipopolysaccharide or LPS)
• Interleukin-1 or Interleukin-2
• β-Endorphins
• Other Lymphokines or monokines
Peripheral and Pulmonary Vascular Effects
1. Vasodilation of both arteriolar and venular vessels.
2. Vasoconstriction
3. Leukocyte (largely neutrophil) aggregation due to C5a. Causes Microembolization.
4. Vascular endothelial cell dysfunction.
Direct Myocardial Effects
1. Decreased LV ejection fraction
2. LV dilatation
3. Abnormal ventricular compliance (Volume/Pressure)
"Cardiovascular Insufficiency"
• Maldistribution of blood flow (patchy, uneven flow)
• Reduced resistance to blood flow
• Lactic acidemia
• Increased mixed venous O₂
Severe Decrease in Systemic Vascular Resistance
(40%)
Severe Myocardial Depression
(10%)
Severe Multiple Organ System Dysfunction
(50%)
Unresponsive Hypotension
Multiple Organ System Failure
Death

Figure 2. This is a schematic diagram summarizing the probable pathogenetic steps involved in human septic shock. (*Revised from* Parker MM, Parrillo JE: Septic shock: Hemodynamics and pathogenesis. JAMA 250:3324–3327, 1983; with permission.)

***Canine Studies.*** We have developed a canine model that simulates the cardiovascular pattern of human septic shock.[32–36] This model attempted to closely approximate the human disease by the following: (1) live bacteria were placed in an intraperitoneal clot to simulate a nidus of infection causing bacteremia as seen in the human disease; (2) large quantities of intravascular volume were given and hemodynamics done both pre- and post-volume infusion to simulate the therapy humans commonly receive, that is, infusion of large quantities of fluid as initial therapy for septic shock; (3) hemodynamic evaluations in the dogs were done serially during a 10-day period since the human form of the disease changes during this period of time; (4) only subcutaneous anesthesia (1 per cent lidocaine) was used during intravascular catheter placements and hemodynamic evaluations since intravenous and inhalation anesthetics may have profound effects on cardiovascular function; and (5) simultaneous radionuclide heart scans and thermodilution catheter hemodynamics were done since (a) this sophisticated method of hemodynamic study well characterized the cardiovascular changes seen in the human form of the disease, and (b) this allows determination of end diastolic ventricular volumes as well as several measures of systolic performance.

After implantation of a peritoneal clot with viable bacteria and adequate volume resuscitation, these animals develop a hemodynamic pattern similar to humans characterized by tachycardia, hypotension, a decrease in left ventricular ejection fraction, left ventricular dilatation, and a normal or increased stroke volume and cardiac index. This animal model has enabled us to do experiments that more closely define the time course and allow quantitation of the important variables underlying the cardiovascular abnormalities of septic shock in humans. In these dogs, the ejection fraction began to fall from the onset of shock and was maximally depressed at 2 to 4 days (see

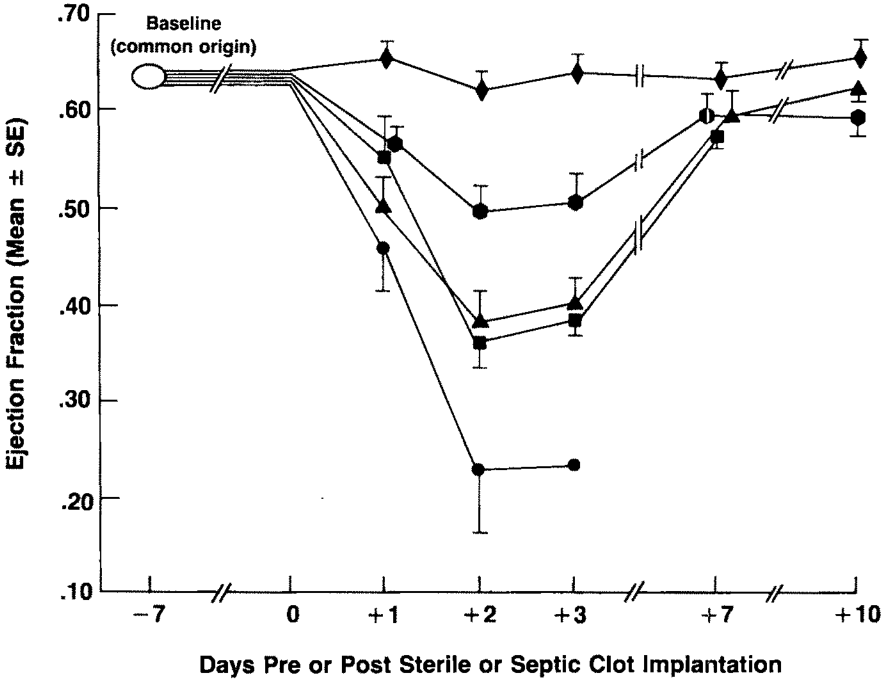

Figure 3. Serial left ventricular ejection fractions in infected dogs and controls as a function of time in days from the implantation of a clot into the animal's peritoneum to simulate a nidus of infection. The symbols stand for different bacteria (*E. coli*) dosage groups: ◆, controls (no bacteria in the intraperitoneal clot); ●, 7 × $10^9$ organisms; ▲, 14 × $10^9$ organisms; ■, 30 × $10^9$ organisms; and ● 30 × $10^9$ organisms in nonsurviving dogs. The baseline represents a presepsis time point before any intervention. Increasing dosages of bacteria at a nidus of infection results in a stepwise decrease in the minimal left ventricular ejection fraction until a minimal plateau is achieved. Further increase in bacterial dose from 14 to 30 × $10^9$ results in death of a number of animals. See text for further details. (*From* Natanson C, Danner RL, Fink MP, et al. Cardiovascular performance with *E. coli* challenges in a canine model of human sepsis. Am J Physiol 254:H558–H569, 1988; with permission.)

Figs. 1 and 3). In survivors, full recovery took approximately 14 to 28 days. These changes in left ventricular ejection fraction correlated to decreases in myocardial function as measured by Frank-Starling ventricular function curves and as quantitated by end systolic volume versus peak systolic pressure plots. Abnormalities of these measures suggest an intrinsic septic shock induced contractility abnormality.[32,33,41]

The septic shock induced left ventricular dilatation occurred between 30 to 40 hours post onset of shock. This dilatation of the left ventricle appeared to be a diastolic compensatory mechanism for the loss of both cardiac chronotropic and inotropic function. The dilatation appears to enable the left ventricle, despite myocardial depression, to maintain stroke volume and cardiac output (Frank-Starling mechanism).[33] In our judgment, dilatation of the left ventricle represents the appropriate physiologic response to direct myocardial depression. Such ventricular dilatation allows maintenance of stroke volume in the face of decreased myocardial cell shortening.[32,33]

Studies in this canine model have helped determine the role of the microorganism in these cardiovascular changes. The number of bacteria at a nidus of infection appears to be an important variable that is directly related in a dose-dependent fashion to the degree of myocardial depression and ultimate lethality (see Fig. 3).[33] In addition, the viability and type of microorganism have profound effects on cardiovascular dysfunction. Viable versus nonviable bacteria and certain species of bacteria are more potent inducers of these cardiovascular changes. However, all bacteria (gram-positive, gram-negative) produce a similar pattern of cardiovascular injury, probably via a final common pathway of injury, but with different potencies to induce these changes in cardiovascular function.[32–35]

One of the most important but controversial questions regarding the pathogenesis of septic shock is whether endotoxin, a lipopolysaccharide present in gram-negative bacteria cell wall, is the universal mediator of these cardiovascular changes and lethality of septic shock. This hypothesis holds that endotoxin from the cell walls of bacteria produces the cardiovascular changes and lethality in gram-negative shock. Further, during gram-positive or fungal sepsis, endotoxin is released from gram-negative bacteria in a patient's "leaky" bowel wall, and this hypothesis argues that endogenous endotoxin is responsible for cardiovascular changes and lethality in gram-positive or fungal shock.[19] However, we have demonstrated using this model of septic shock that gram-positive bacteria have no detectable endotoxin but gram-positive bacteria can produce the exact same cardiovascular profile as gram-negative bacteria. Circulating endotoxin was shown to be absent by using a sensitive chromogenic substrate limulus lysate test and by drawing blood samples very frequently.[15] Thus, endotoxin is not the universal mediator of septic shock, but probably it represents one of the multiple bacterial exotoxins and mediators that are inducers of a common pathway of cardiovascular dysfunction in septic shock.[14,15,35]

Very recently, using this canine model of human septic shock, experiments were done to determine the effect of therapeutic maintenance of cardiovascular stability on morbidity and mortality.[36] A comparison was made among the following groups: no therapy; therapy with antibiotics alone; therapy with fluids and/or dopamine to maintain an adequate mean arterial pressure; and therapy with both antibiotics and fluids/dopamine. None of 11 animals receiving no therapy survived (survival percentage = 0 per cent). One of eight (13 per cent) receiving antibiotics alone, and one of eight (13 per cent) receiving fluids/dopamine support alone survived. Nine of 21 (42 per cent) animals receiving both therapies survived. In a controlled study, this investigation demonstrates that antibiotics and fluid/dopamine maintenance of blood pressure are both efficacious when employed together. A probable explanation of this outcome is that each therapy can only reverse the pathogenetic process if the other therapy is also given, that is, both exert a permissive effect on one another.[36] This data emphasizes the need to institute both effective antibiotics and effective cardiovascular support to optimize the therapeutic outcome in septic shock.

### Pulmonary Damage

Septic shock induced pulmonary damage may vary from mild dyspnea and tachypnea to severe pulmonary damage and hypoxemia requiring mechanical ventilation.[1] Respiratory failure associated with septic shock, the adult respiratory distress syndrome (ARDS), is characterized by hypoxemia, diffuse pulmonary infiltrates with normal left ventricular filling pressures.[1] It is estimated that more than half of people with severe septic shock may go on to develop ARDS. The ability of modern mechanical ventilation with positive end expiratory pressure to maintain oxygenation and ventilation has made primary respiratory failure an unusual cause of death in septic shock. However, respiratory failure often becomes part of a syndrome of multisystem organ failure (commonly a combination of renal, hepatic, and CNS failure) leading to patient demise.

One hypothesis regarding the pathogenetic mechanism of pulmonary damage in septic shock induced ARDS states that "aggregating neutrophils" release toxic substances into the pulmonary circulation and produce endothelial cell damage leading to microcirculatory insufficiency and further pulmonary parenchymal damage.[11,12] However, recent data demonstrated that ARDS can occur in septic severely neutropenic patients indicating that the aggregating neutrophils hypothesis cannot explain the mechanism of ARDS in all patients with this form of sepsis associated pulmonary dysfunction.[37]

Septic shock patients with respiratory failure are commonly maintained in intensive care units with mechanical ventilation. Such patients frequently have dysfunction of other organ systems necessitating major technical interventions such as dialysis for renal failure. This patient is at bed rest with multiple catheters in different body parts, that is, intravascular, endotracheal, intrabladder, and nasogastric catheters are frequently employed. This places the patient at risk for recurrent opportunistic infection, recurrent bouts of septic shock, and worsening organ dysfunction. If not reversed, such a sequence may ultimately lead to irreversable multisystem organ damage and death.

## OTHER ORGAN SYSTEM DYSFUNCTION

It should be remembered that septic shock is a systemic disease affecting all the blood vessels and the organs in the body. Different organs may be more damaged than others. In the kidneys, dysfunction ranges from mild elevations of serum creatinine to anuric renal failure requiring dialysis. Hepatic dysfunction is most commonly evidenced by elevations of bilirubin with relatively normal transaminases. Thrombocytosis, thrombocytopenia, leukocytosis, leukopenia, and disseminated intravascular coagulation are only some of the wide range of hematologic abnormalities that may occur. It is not known what factors determine which organs are damaged and the degree of damage. It may be related to the predisposition of the host, a propensity of a particular infecting microorganism, or a combination of host and microorganism issues. However, it should be remembered that this disease is systemic and requires a full evaluation of every organ system with potential need for supportive care.

## DIAGNOSIS AND THERAPY

Septic shock therapy demands treatment of a generalized process. Therapy has three different goals: (1) to eradicate the septic nidus; (2) supportive care for the multiple organ systems involved; and (3) administration of agents that can neutralize or reverse the effects of septic shock induced toxins.

Once the diagnosis of septic shock is suspected, the rapidly lethal nature of this disease requires immediate therapy to eradicate the infection and stabilize the cardiovascular systems. The diagnosis of septic shock should be suspected in patients who develop fever, hypotension, leukocytosis, with a possible focus of infection.[42] Arterial and pulmonary artery catheterization can give confirmatory evidence by documenting hypotension associated with a decreased systemic vascular resistance, a high or normal cardiac output, and, commonly, a high mixed venous oxygen saturation. Empiric antibiotic therapy with coverage for gram-positive and gram-negative microorganisms should be started immediately. The antibiotic regimen chosen should assure coverage of all likely microorganisms based on the usual causative organisms in a given clinical setting in a given hospital environment. Since survival is higher if the empiric antibiotics are effective against the microorganism isolated,[51] the antibiotic regimen should be initially broad to assure coverage. Once the causative organism is known, the antibiotic spectrum can be narrowed.

Once the diagnosis is suspected and antibiotics begun, the site of infection should be identified. Infected foreign bodies may need to be removed and pus collections identified and surgically drained. However, despite a thorough diagnostic evaluation, the site of infection is often not found especially in neutropenic or severely immunocompromised patients. These infections are probably due to small intraabdominal or pulmonary foci difficult to diagnose with our present technology.

The supportive care of septic shock is usually aimed at normalizing septic shock induced laboratory abnormalities. The hypotensive patient should be given large qualities of intravascular volume guided by pulmonary artery catheterization to normalize left ventricular filling pressors. Catecholamines, most often dopamine and norepinephrine, may be given if volume administration fails to return the mean arterial pressure to near normal values. Initially, hypoxemia may be treated with supplemental oxygen. However, lung disease may progress to require intubation and mechanical ventilation in addition to positive end expiratory pressure (PEEP) to aid oxygenation. PEEP is an important adjunct to ventilatory support in the patient with ARDS since it allows adequate oxygenation at nontoxic levels of oxygen therapy.[23] The hematologic, metabolic, renal, and hepatic function need to be carefully monitored for other possible therapeutic interventions.

Therapy with antibiotics, surgical drainage, and supportive care remain the mainstays of present-day therapy. Data derived from retrospective human studies suggest that full-time critical care physician and nursing staffs with modern technology for cardiovascular support can result in enhanced survival of septic shock patients.[23,29] Prospective animal studies show the importance of fluids and dopamine to maintain an adequate blood pressure, and antibiotic therapy to eradicate the causative microorganism.[36]

High-dose glucocorticosteroids,[6,47] a therapy in widespread clinical use until recently, has been shown to be of no value in the majority of patients with septic shock and may even have a detrimental effect in some subgroups of patients with established renal insufficiency. New therapies using immune plasma from volunteers vaccinated against the J5 *Escherichia coli* mutant has been shown to alter the clinical course of septic shock and decrease mortality in humans.[52] However, this agent is not generally available, and its therapeutic application remains controversial. Other investigational therapies such as naloxone,[24] prostaglandin inhibitors,[21,22,25] lipid X,[14,43,44] and antibodies to cachetin[3] have been shown to prevent mortality in animal models, but their clinical efficacy in human septic shock is unknown. Lipid X, 2,3 diacyl glucosamine 1-phosphate is a monosaccharide precursor in the biosynthetic pathway of endotoxin[14,43] with unique antiendotoxin properties.[14] Lipid X is structurally related to lipid A, the toxic moiety of endotoxin, but has been shown to protect mice[43] and sheep[44] from lethal challenges of endotoxin. In vitro investigations demonstrated that lipid X can block the effect of endotoxin on neutrophils in a dose-dependent manner. Increasing concentrations of lipid X decrease the endotoxin response of neutrophils to endotoxin.[14] Lipid X may provide a novel approach to the treatment of those patients with septic shock in whom endotoxemia plays a role.

## SUMMARY

Septic shock is characterized by bacteremia and/or toxemia and hypotension. It is commonly a nosocomial disease that is the leading cause of death in intensive care units in the United States. The disease can result in profound cardiovascular instability, and it can also result in a syndrome of multiple system organ dysfunction. Death can also result from progressive hypotension (due to either a severe decrease in cardiac performance or a severe decrease in systemic vascular resistance) or patient demise can occur due to multiple organ system failure, a syndrome that can result in failure of lungs, kidneys, brain, liver, or heart.

This disease probably results from the ability of microorganisms to cause the release of a number of mediators that have profound effects on microvasculature, myocardium, and perhaps other tissues. This is a systemic disease and every organ system may be affected. Despite the availability of effective antibiotics that can eradicate most of the infecting microorganisms, the mediators released cause enough damage to result in a high patient mortality. Although current therapy of this syndrome (with cardiovascular support and antimicrobial agents) has resulted in increased patient survival, future emphasis must be placed on characterizing and ultimately reversing the effects of the potent vasoactive circulating mediators of this disease.

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# Cardiovascular Dysfunction in Multisystem Organ Failure: Focus on Septic Shock

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Since sepsis is the most common clinical syndrome preceding multisystem organ failure (MSOF), and a frequent finding in critically ill patients with other primary insults, priority in this article will be given to cardiovascular pathophysiology of septic shock.

The derangement of vasomotion and ventricular function that occurs in septic shock remains controversial more than 35 years after Waisbren's description of such patients as "appear(ing) . . . hot, dry, and flushed, (with) . . . pulses full and bounding" or "cold, clammy, and lethargic."[224] Since then, investigators have asked whether distinct physiologic patterns exist in these patients[76,78,95,156,164,227,228,233] or if this represents a continuum of the hemodynamic response. The prognostic value of this apparent dichotomy has received increasing attention recently, as has its therapeutic implication.

The understanding of this hemodynamic response is essential since septic shock remains the leading cause of death in medical and surgical intensive care units (ICUs). Some 300,000 patients develop gram-negative bacteremia annually, with mortality from septic shock syndrome, which occurs in 40 to 50 per cent of cases, ranging from 40 to over 90 per cent and usually in the neighborhood of 60 per cent. This figure may appear excessive, although it compares favorably with cardiogenic shock, where mortality is usually greater than 90 per cent and has not changed in 20 years.[60] The institution of ICUs has been associated with reduction in mortality from the 82 to 96 per cent in the pre-ICU era.[159] The staffing of ICUs with physicians experienced in invasive monitoring may also be having an impact.[106] Although early investigators focused on the hemodynamic derangements caused by specific organisms, the consequences and mortality of septic shock are identical and independent of its etiologic agent,[168,230] which speaks for a common pathophysiologic response of the body to over-

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whelming sepsis. Mortality patterns seem to be divided almost equally between MSOF and refractory vasodilation, with some 10 per cent of patients dying with myocardial failure. The majority of patients with MSOF manifest persistent vasodilation. The incidence of major associated system failure, noncardiac pulmonary edema, ranges from 25 to 38 per cent with associated mortality in excess of 50 per cent.

## OXYGEN METABOLISM

Shock is the failure to meet tissue oxygen demand due to failure of delivery or utilization; septic shock may be a combination of both. Delivery may be limited due to cardiac dysfunction or reduced oxygen content, while peripheral extraction shows both global and regional disturbances as well as pathologic dependence of oxygen consumption ($VO_2$) on oxygen delivery ($DO_2$). Since this is of therapeutic and prognostic importance, disorders of oxygen metabolism will be addressed first.

In normal subjects $VO_2$ is protected in the face of dropping $DO_2$ by increased tissue oxygen extraction. Widened arterial-venous oxygen content difference ($DAVO_2$) and reduced mixed venous oxygen saturation ($SVO_2$) are seen. $VO_2$ and $DO_2$ become directly dependent below critical $DO_2$, which has been found to occur at oxygen extraction ratio (OER) of approximately 0.7 to 0.8 or oxygen delivery of less than 7 to 9 ml per kg per minute. Anaerobic metabolism and lactic acid production occur, even though a simple relationship with derangements of $VO_2$ cannot be documented. Tissue oxygen extraction seems to be impaired in sepsis. Pathologic supply dependency of oxygen uptake occurs; recent experimental studies of canine bacteremia show that oxygen consumption becomes dependent on oxygen delivery in a much higher range of $DO_2$ (more than 50 per cent above control) with extraction ratio close to 0.5.[137] The hallmark of severe human septic shock is a low $DAVO_2$ and decreased $VO_2$, in the face of normal or increased cardiac output[200,201] more likely due to arteriovenous shunting rather than impaired cellular ability to utilize delivered oxygen.[72,90]

Considerable literature dealing with adult respiratory distress syndrome (ARDS), the most commonly occurring severe end organ failure associated and overlapping with sepsis, suggests that similar derangement in peripheral oxygen utilization exists. An OER of 0.3 is seen in association with low $DAVO_2$ and high $SVO_2$, a finding commonly seen in septic shock. Supply dependency of oxygen consumption on oxygen delivery shows a plateau of 2.5 to 3 times greater than in non-ARDS patients and occurs at $DO_2$ levels around 21 ml per kg per minute.[118] For any given level of $DO_2$, the $VO_2$ is less than in patients without ARDS and remains supply dependent at much higher levels. This pattern may be due to loss of autoregulation, peripheral microembolization, or other mechanisms resulting in increased diffusion pathway and maldistribution of oxygen delivery.

Derangement of oxygen utilization (decreased $VO_2$), and the change in systemic oxygen consumption relative to delivery, does not merely reflect a physiologic marker of septic shock, but also has important negative prognostic implications.[90,201,221,235]

Several investigators[72,90,235] have shown that patients in septic shock respond to fluid loading with increased $DO_2$, increased $VO_2$, and in some cases reduction in serum lactate. This response is greatest in patients with increased baseline serum lactate, and therefore, may reflect the ability of increased volume loading to correct either defective oxygen utilization or inhomogenity of delivery, with the latter being more likely. The ability to increase $DO_2$ and $VO_2$ with volume infusion is associated with successful resuscitation and high survival in septic shock.

Physiologic derangements in sepsis can be documented almost 24 hours prior to hemodynamic decompensation. Abraham[3] has studied this issue and documented that significant reduction in $DO_2$, $VO_2$, and systemic vascular resistance (SVR) occur many hours prior to the onset of shock and may remain depressed for 2 days after adequate resuscitation of blood pressure. A follow-up report addressing the issue of preshock physiology as a predictor of survival has shown[4] that the likelihood of survival from septic shock is related to the ability to produce a greater increase in $DO_2$, $VO_2$, cardiac index, and left ventricular stroke work index (LVSWI) 8 hours prior to decompensation.

Nonseptic critically ill patients do not usually exhibit supply dependency and respond to increased $DO_2$ with reduction in $DAVO_2$ while $VO_2$ remains fixed. Survival in sepsis may be enhanced by a higher increment of $VO_2$ in response to a rise in cardiac output.[235] Manipulation of $VO_2$ may be a two-edged sword with insufficient tissue energy production and excessive toxin generation with high $VO_2$ on one side, and perfusion dependent organ system failure with depressed $VO_2$ on the other.

Overall, $DO_2$ of sepsis is increased, and its absolute level regulates $VO_2$. Peripheral shunting at the microvascular level is evident. The ability to normalize oxygen consumption may be associated with high survival. Lactic acidosis may predict better response to fluid resuscitation; increased $VO_2$ due to improved distribution of $DO_2$ together with reduced lactate, possibly more efficiently cleared by the hepatic and renal route, are seen. Failure to do so is followed by progressive vasodilation, narrowing of $DAVO_2$ and refractory depression of oxygen extraction. This pattern is associated with progression to MSOF.

Since increased oxygen delivery may augment peripheral utilization and decrease anaerobic metabolism, emphasis should be placed on understanding and correcting derangements of ventricular performance in septic shock.

## HEART IN SEPSIS: MECHANICS, PERFUSION, AND METABOLISM

Myocardial performance is primarily dependent on three interrelated factors: preload, afterload, and contractility. It is helpful to have a fundamental understanding of these parameters when considering the heart in MSOF.

Since Bowditch's pioneering work on the interval-strength relationship of myocardial fibers in 1869, it has been known that the initial length of these fibers will alter their performance. In 1884 it was demonstrated in heart-lung preparations that increased venous return resulted in increased stroke volume (SV). In 1895 Frank demonstrated that cardiac preload is related to contractility in the isolated frog ventricle.

These and other investigators demonstrated in essence that ventricular contraction was related to fiber length during the time period immediately preceding systole. Over the years investigators extrapolated this principle and have determined a linear relationship between left ventricular end diastolic volume (LVEDV) and SV.

Clinically, however, it is difficult to obtain ventricular volume parameters; hence, left ventricular end diastolic pressure (LVEDP) has been used. This requires a left heart catheter, which is not readily available at the bedside. The fact that a "wedge" pressure obtained in a pulmonary artery gave pressures in the pulmonary venous system was first demonstrated by Hellems[73]; correlation of pulmonary artery occlusion pressures with left atrial pressure (LAP) was demonstrated later. Years later, the notion of a balloon tipped PA flotation catheter that could be inflated or deflated to give alternating PA systolic and diastolic pressures or PA occlusion pressure (PAOP) became a reality through the work of Swan and Ganz.[216] Numerous investigators have demonstrated excellent correlations between PAOP and LAP,[53,98,226] however, the correlation between LAP and LVEDP is not as strong.[178] Rahmtoola showed that in patients with acute myocardial infarction, LVEDP was in large part due to atrial contraction. It was felt that atrial contraction increased LVEDP without significantly increasing mean LAP or thus PAOP. Other investigators have reported similar findings.[57] In terms of clinical availability at the bedside, we are left with PAOP that correlates well with LAP, but may not correlate well with LVEDP. Furthermore, because of differences in ventricular compliance and intrapericardial or intrathoracic pressures, there may be disparity between intraventricular pressures and volumes.

Contractility is a difficult property to accurately define. One may define contractility as "the state of performance that the myocardium achieves with the circulation at a basal state and with normal end diastolic volume or pressure and PAOP."

Work by Sonnenblick and others[1,210,211] has demonstrated that contractility appears to be related to velocity of contraction without change in fiber length. Since one is dealing with changes in velocity, changes in contractility are best demonstrated through changes in forced volume curves. These curves can be determined for the human heart.[96] However, it became evident that determinations made in this fashion were no more reliable than left ventrical ejection fraction (LVEF).[18] Thus, force-velocity curves have not made a strong clinical impact in assessment of contractility. As shown initially by Sarnoff and Mitchell,[188] changes in contractility can be demonstrated by ventricular function curves, though these are not as sensitive as force-velocity measurements.[80] Ejection fractions by nuclear ventriculography also provide some information about contractility. However, ejection fraction is not strictly a function of change in fiber length. Numerous variables can affect the determination.[51,91,215]

Afterload refers to the overall resistance against the heart during systole. Afterload has a number of components including peripheral vascular resistance, blood viscosity, and aortic impedance.[19] In addition, because of LaPlace's law, the EDV and hence EDP play a significant role in afterload. Clinically, we use total peripheral resistance (TPR) as a measure of afterload, but this may not be a very accurate measure. The concept of afterload is important in assessing LV function. Changes in afterload can make a normally contracting ventricle appear depressed in terms of overall cardiac performance. Conversely, an impaired ventricle can perform better than one would expect because of afterload decreases. This concept of "afterload mismatch" was described by Ross[183] and is typified by the situation in chronic mitral regurgitation where the regurgitant flow functionally results in a decreased preload. The subsequent determinations of LV functions (for example, LVEF) may overestimate the actual contractile state, and after valve replacement there is often a deterioration in LV function. A similar situation exists in sepsis where it appears that myocardial function is depressed, though the overall circulatory picture is a hyperdynamic one with higher than normal cardiac output.

It is clear that cardiac output or index is not a reliable index of performance in hyperdynamic patients. Since end diastolic pressure (PAOP), is not related to ventricular end diastolic volume in a fixed manner in critically ill patients (that is, ventricular compliance is dynamic and changing), the relationship of cardiac performance to wedge pressure is equally unreliable. Thus, the sine qua non of bedside cardiac function is not as useful as one might expect in patients with septic shock.

As discussed later, two parameters that have been of increasing value in analyzing cardiac performance in septic patients are ventricular ejection fraction[64,145,155,164] and the response of ventricular performance to volume loading. These parameters are not merely reliable indicators of myocardial function, they may prognosticate outcome in septic shock.

The final aspect of ventricular function not to be forgotten prior to detailing specific derangements in septic shock is that of ventricular diastolic function. Within the past 5 years it has been shown that diastolic relaxation and diameter may determine outcome in patients with ischemic as well as hypertensive heart disease. This may also be true of cardiac dysfunction in septic patients.

Our current understanding of appropriate hemodynamic evaluation in critically ill patients with sepsis has been expanded. Systolic function is probably best examined at the bedside by following serial radionuclide LVEF or Starling curves, using LVEDV as a valid measure of preload, related to left ventricular pressure work defined as LVSWI. Response to standardized fluid challenge can be analyzed and end diastolic pressure-volume relationship studied, providing valid information as to the ventricular compliance properties.

## Pressure and Flow

Since Waisbren's description in 1951, septic shock has been described as either a hypodynamic state or a hyperdynamic state, with an elevated cardiac output, a markedly decreased systemic vascular resistance, and a variable ventricular filling pressure. Early studies on patients with septic shock appeared to indicate that these two distinct hemodynamic patterns existed.[76,157] The high incidence of hypodynamic sepsis seen until some 20 years ago was most likely due to inadequate volume resuscitation and left ventricular preload.

The earliest studies of septic shock attempted to analyze the hemodynamic profiles seen in these patients. Udhoji[220] and Siegel[197] show two distinct hemodynamic patterns in patients with septic shock. Siegel concluded that there is a valid basis for separation of patients into hyperdynamic and hypodynamic groups.[78] The relationship of hemodynamic profile and volume status was evolving. Udhoji's patients with decreased cardiac indexes and vasoconstriction exhibited smaller total plasma volumes than the hyperdynamic group.[220]

Wilson[237] described hemodynamic patterns of cardiogenic, hypovolemic, septic, and complicated (mixed) shock. The patients with septic shock predominantly displayed normal or elevated cardiac indexes and decreased TPR. The patients with mixed septic and hypovolemic shock displayed normal or low cardiac indexes and variable TPR.

Wilson showed that patients with pure septic shock had elevation of their cardiac index and uniform decrease in vascular resistance. There was a more variable hemodynamic response in patients with hypovolemia and sepsis, with an increased trend for hypodynamic-vasoconstricted parameters in hypovolemic patients. Nishijima[55] studied the hemodynamics of patients with gram-negative bacteremia and decreasing blood pressure. He noted that there was a difference in the hemodynamic patterns of survivors and nonsurvivors. Survivors had a high cardiac index, lower vascular resistance, higher plasma volume, and a higher total blood volume. There were two distinct hemodynamic patterns in patients with septic shock, hyperdynamic-vasodilated (survivors) and hyperdynamic-vasoconstricted (nonsurvivors). Patients with hypodynamic profiles had decreased volume status. Central venous pressure (CVP) did not differ in the two groups, although volume status was significantly different.

In summary, early investigators have demonstrated two distinct hemodynamic patterns in patients with septic shock. There is a relationship between total intravascular volume and hemodynamic state, with hypovolemic patients more likely to display hypodynamic profiles and higher mortality. The CVP was often used to reflect preload in these early studies, however, it is a poor indicator of vascular volume or left ventricular preload. Weil[227] reviewed the relationship between cardiac index and total blood volume in patients with gram-negative septic shock. These 30 pooled patients showed a direct correlation between these two parameters, which was independent of therapeutic intervention.

The difficulties of early studies arise from overcautious use of volume resuscitation because of exaggerated concern for worsening of pulmonary dysfunction of sepsis (ARDS) in the face of inadequate hemodynamic monitoring capabilities. Bedside availability of balloon tipped pulmonary artery catheters resulted in safer and more vigorous volume resuscitation as well as reduced incidence of early hypodynamic sepsis.

Having shown that there is a relationship between intravascular volume and hemodynamic profile, subsequent investigators attempted to qualify the relationship between LVEDP, as reflected by PAOP, and hemodynamic state. They have suggested that there is a limit to the increase in cardiac output with increasing intravascular volume, after which cardiac output remains fixed or declines.[146,228,234] These studies have attempted to produce guidelines as to the optimal LVEDP as well as analyzing ventricular competence in terms of volume and pressure work as related to volume infusion.

Rapid, adequate, and safe volume resuscitation in sepsis is crucial. The goals are restoration of effective blood volume, left ventricular output and resulting $DO_2$, without increased pulmonary capillary hydrostatic pressure. The latter variable is clinically estimated as pulmonary artery occlusion pressure (PAOP). This is not necessarily correct; pulmonary capillary pressure is located some 40 per cent upstream from pulmonary venous pressure, which the PAOP estimates and is subject to variations independent of pulmonary artery and venous pressure. Our ability to adequately measure PAOP in critically ill patients is marginal at best; the use of pleural pressure monitoring, attention to lung mechanics and the effects of respiratory care methods[109] and the use of muscle relaxants[199] have improved our ability to measure this essential variable.

Overall, there is no consistent relationship between PWP and left ventricular preload (LVEDV).[25] Many of the studies looking at the response of left ventricular output to manipulation of PAOP with volume challenge are hampered by the inability to assess the contribution of changing ventricular compliance as well as the frequent lack of appropriate controls.

In studies by Winslow[234] and Weisel,[228] patients in septic shock responded to volume expansion with an increase in cardiac index and stroke work index (LVSWI) and a decrease in systemic vascular resistance. In Weisel's study optimal wedge was achieved at a PAOP of 10 to 12, at which point further increase in PAOP resulted in diminished LVSWI. Nonsurvivors achieved their maximal LVSWI at a slightly higher PAOP and maximal LVSWI was lower in these patients.

The establishment of hyperdynamic patterns after volume expansion in previously hypodynamic individuals has also been demonstrated in animal models of endotoxin shock.[26,127,218]

The optimal PAOP to be achieved with volume resuscitation was further discussed by Packman,[146] in 15 hypovolemic and septic shock patients; maximal LVSWI occurred at a PAWP of 11 to 12 mm Hg. Although the direction of change in wedge correlated with initial PAOP in this study, changes in the value of CVP did not correlate with changes with PAOP as repeatedly shown by others in critically ill patients.

While most investigators have noted a relationship between LVSWI and intravascular volume, this uniform increase in cardiac function with volume resuscitation has not been noted by others.[68,95,139] Intravascular volume status and ventricular response to fluid loading in sepsis were felt to be of prognostic significance with high mortality in patients with myocardial depression.

## Cardiac Volume Measurements

Bedside availability of nuclear ventriculography greatly expanded our understanding of biventricular function in sepsis; systolic and diastolic function, regional and global contractility, and dynamic compliance can now be studied.

Myocardial dysfunction during septic shock has been alluded to by many investigators in both animal and clinical studies.[119] Since estimates of left ventricular preload are often difficult at the bedside, and ventricular compliance in critically ill patients is dynamic, investigators have recently used cardiac imaging techniques to demonstrate relative changes in systolic and diastolic function in examining myocardial performance in sepsis. Cardiac index may not adequately reflect myocardial performance, since tachycardia may mask depression of myocardial function. Stroke volume index (and stroke work index) does not evaluate cardiac dimension, nor tell if overall cardiac performance is maintained only because of elevated LVEDV. Ejection fraction, as determined by nuclear cardiography or echocardiogram, on the other hand, may help demonstrate areas of global and segmental myocardial dysfunction, is a good prognosticator of mortality in ischemic heart disease,[71] and may be helpful in early management and prognostication of patients with septic shock.

Calvin[24] was not able to demonstrate consistant abnormalities in LVEF during volume expansion in a group of patients with sepsis without shock even though he identified a subset of patients with depressed LVEF. Ognibene[139] in a study using appropriate controls and combined invasive and noninvasive techniques showed that patients with septic shock demonstrate significantly depressed myocardial contractility, which can be seen to a lesser degree in septic patients without shock. Similar volume infusions resulted in comparable increases in PAOP and LVEDV. Patients with septic shock, and to a lesser degree with sepsis without shock, showed greatly reduced response in LVSWI and LVEF.

It would appear intuitively obvious that a patient with an increased cardiac output and ejection fraction would do better than one with decreased cardiac output, diminished ejection fraction, and global or regional myocardial dyskinesis. Although this premise appears logical and has been suggested in some studies of hemodynamics and survival in patients with septic shock, it has not uniformly held true. Parker, from the NIH group headed by Parrillo, presented data[154,156,157] that question this assumption. Fifty consecutive patients with septic shock and positive blood cultures were evaluated; 38 per cent of these patients survived. All patients displayed elevated cardiac indexes, decreased systemic vascular resistance, and normal stroke volume indexes. Twenty-four hours after admission, survivors had decreased cardiac indexes into the normal range, while nonsurvivors continued to have elevated cardiac indexes. Of the nonsurvivors, only a third had relatively decreased cardiac indexes and elevated systemic vascular resistances. Of possibly more significance, no single hemodynamic parameter derived from right heart catheterization at presentation seemed to predict survival.

Subsequently, these investigators performed serial simultaneous invasive hemodynamic and nuclear ventriculography evaluations of 20 patients with septic shock. After volume expansion to a PAOP of 12 to 15, all patients displayed normal or elevated cardiac indexes. Initial cardiac indexes at presentation and the average of cardiac indexes during the first 4 days of admission revealed a trend toward increased values for nonsurvivors. Although stroke volume index did not differ between the two groups, the 13 survivors had decreased ejection fractions. The ejection fraction remained depressed for 4 days and then returned to normal. The nonsurvivors had normal cardiac indexes at presentation and when studied within 24 hours of death. Survivors appeared to dilate their left ventricles while nonsurvivors did not or could not. Although the ventricles of survivors were dilated and able to eject a similar stroke volume to those of nonsurvivors, they required a decreased fraction of total end diastolic volume to do so. It was concluded that a low initial ejection fraction is associated with higher survival and that dilatation of LV is an appropriate response to depressed contractility, which allows for maintainance of SV by Frank-Starling mechanism. Overall, the majority of nonsurvivors demonstrated severe vasodilation and increased cardiac output in contrast to the high mortality, hypodynamic profile of sepsis from the 1960s.

Natanson[127] has recently studied cardiac mechanics in a canine model of sepsis simulating human physiologic derangements. Volume infusion produced hyperdynamic circulation. On days 1 to 4, LVEF dropped to 0.20 to 0.30, and this finding was independent of volume as was ventricular dilatation. Depressed Starling curve on day 1 was reversible with fluid loading; on day 2 contractility was depressed and unresponsive to preload expansion. Maximal increase in left ventricular compliance and dilatation were seen on day 2.

It was postulated that severe fatal septic shock, and the end organ damage that is associated with it, is preceded by myocardial edema, which restricts the failing septic heart. Myocardial edema in septic shock has been confirmed pathologically by other investigators.[174]

This same group has postulated that myocardial depression in septic shock may be due to a substance that they have isolated from the acute phase sera of patients with septic shock[163] that depressed contractility of myocytes in a dose-dependent fashion. Other investigators have also postulated the existence of a myocardial depressant factor (MDF)[99,107,112] and proposed a pancreatic origin for it.

The fact that the septic heart displays reversible diffuse and segmental dyskinesis has been confirmed by other investigators.[49,50] Ellrodt's initial studies concluded that reversible segmental wall motion abnormalities frequently occurred in high output septic shock without evidence of coronary artery disease. Patients with segmental wall motion abnormalities appeared to have a better prognosis than global wall motion abnormalities. Subsequent evaluations in volume resuscited patients with sepsis showed a depressed Starling curve in 94 per cent and LVEF in 54 per cent of subjects; some 63 per cent of the patients had segmental wall motion abnormalities, while 31 per cent of the remaining patients had global abnormalities. Again, patients with decreased ejection fraction displayed increased left ventricular end diastolic diameters. This study supported Parker's findings that in septic shock there is an element of reversible contractile dysfunction. No relationship between conventional measures of hemodynamic performance and survival was seen. In contrast to Parker's data, no relationship between ejection fraction, LVSWI, or the incidence of segmental wall motion abnormalities and survival was seen. The patients in Ellrodt's study were older, had a higher incidence of cardiac disease, lower incidence of malignant disease, were less often treated with corticosteroids, and less likely to be treated with adrenergic pressor agents. This may account for some of the differences between these two studies.

These initial studies of serial cardiac imaging in patients with sepsis have failed to show a correlation between PAOP, cardiac index, systemic vascular resistance, and survival. They confirm that the presence of reversible myocardial depression and occurrence of decreased ejection fraction, with areas of segmental and global dyskinesis, are common. It is a matter of controversy as to whether patients with segmental dyskinesis and decreased ejection fraction in sepsis have better prognosis; however, these patients clearly appear not to have a worse prognosis. Lastly, it is unclear if patients without ventricular dilatation, with higher ejection fractions, and with decreased ventricular compliance are simply primarily exhibiting the effects of myocardial edema or if this represents the cardiac manifestations of a refractory peripheral vascular derangement of sepsis.

The nuclear ventriculography data offer insight into pump dysfunction in sepsis but have not had a major impact on patient care or prognostic care in clinical institutions.

Recent reevaluation of data by an NIH group[258] suggests that standard hemodynamics may be of prognostic use after all. Initial heart rate less than 106 beats per minute was a strong positive prognostic indicator as was the ability to reduce heart rate by more than 18 bpm below 95 bpm, increase SVRI above 1529 dync sec/cm$^5$, and to decrease CI by more than 0.5 L/min/m$^2$ at 24 hours.

## MYOCARDIAL PERFUSION AND METABOLISM

Cardiac dysfunction may be the result of hypoperfusion and inadequate $DO_2$, myocardial depressant substance, or derangements in cardiac substrate metabolism.

Coronary arteries deliver some 80 to 180 ml per minute of blood to the myocardium at mean arterial pressure of 90 mm Hg with left ventricular coronary blood flow of 6 to 15 ml per 100 gm of muscle. Of coronary sinus venous blood flow, 83 per cent comes from the septum and LV free wall. When LV work and myocardial oxygen consumption ($MVO_2$) are kept constant and perfusion pressure varies, coronary vascular resistance changes to maintain coronary blood flow (CBF) constant; autoregulation operates in the perfusion pressure range of 60 to 130 mm Hg and is mediated metabolically. As mean arterial pressure drops below 60 mm Hg length of diastole and coronary perfusion pressure becomes crucial. $MVO_2$ (8 to 10 ml per 100 gm per minute) responds to changes in contractility, heart rate, and myocardial wall stress and affects CBF in linear fashion.

Myocardial hypoperfusion has been proposed as one of the etiologies of cardiac dysfunction in septic shock. Several early animal studies have indicated that myocardial hypoperfusion may occur in the setting of endotoxin induced shock.[9,77,93]

This appeared to be out of proportion to the degree of systemic hypotension, and decreased coronary perfusion pressure did not exclusively explain this apparent myocardial ischemia. Inhomogeneous perfusion of the myocardium with relative subendocardial ischemia has been also cited as a causative factor for cardiac dysfunction in the canine endotoxin shock model.

Other investigators have pointed to transient ST-T wave changes from electrocardiograms of patients without obvious artherosclerotic heart disease as possible evidence of transient ischemic episodes in the setting of septic shock.[217]

Two clinical studies have prospectively addressed coronary circulation in patients with septic shock using coronary sinus catheterization. Neither of these studies demonstrated defective coronary blood flow. Cunnion[37,38] has documented normal $MVO_2$ in the face of decreased arterial-coronary sinus content difference, decreased myocardial oxygen extraction ratio, and increased coronary sinus blood saturation. Profound coronary vasodilation and net lactate extraction were seen. There was no relationship with myocardial depression (low LVEF) or the use of catecholamines. Myocardial ischemia was not documented while the oxygen metabolism pattern closely paralleled that of systemic oxygen utilization in septic shock. Dhainaut[45] addressed the issue of myocardial substrate metabolism. Overall physiology was characterized by low ventricular volume work, tachycardia, coronary vasodilation with high coronary blood flow, elevated myocardial lactate extraction, and depressed utilization of free fatty acids, glucose, and ketones. $MVO_2$ and its relationship to cardiac workload was not different from nonseptic controls; some 41 per cent of myocardial oxygen consumption could not be explained by the utilization of commonly available exogenous substrates. Nonsurvivors were characterized by higher heart rates, systemic lactates, coronary sinus blood flows, and more profound reduction in the contribution in free fatty acids, glucose, and ketones as energy sources as well as the deficit in calculated energy (55 per cent). Myocardial lactate production signifying cardiac ischemia was identified in 15 per cent of these patients.

The relationship of derangements in cardiac oxygen and substrate metabolism to cardiac mechanics and the role of metabolic intervention are not well understood.

## Energy Generation

Energy generation in the myocardium occurs through an interplay of various fuel pathways (Fig. 1). Glucose, fatty acids, triglycerides, lactate,

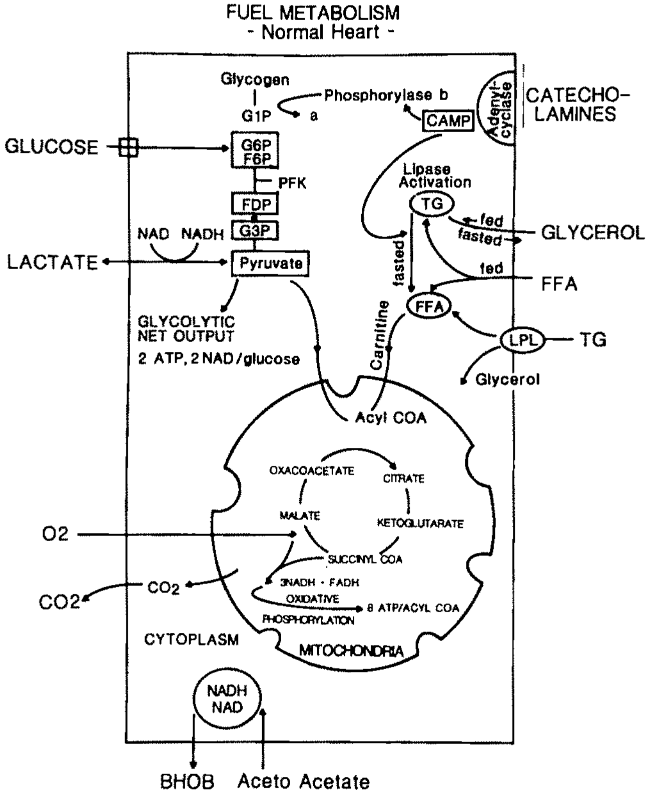
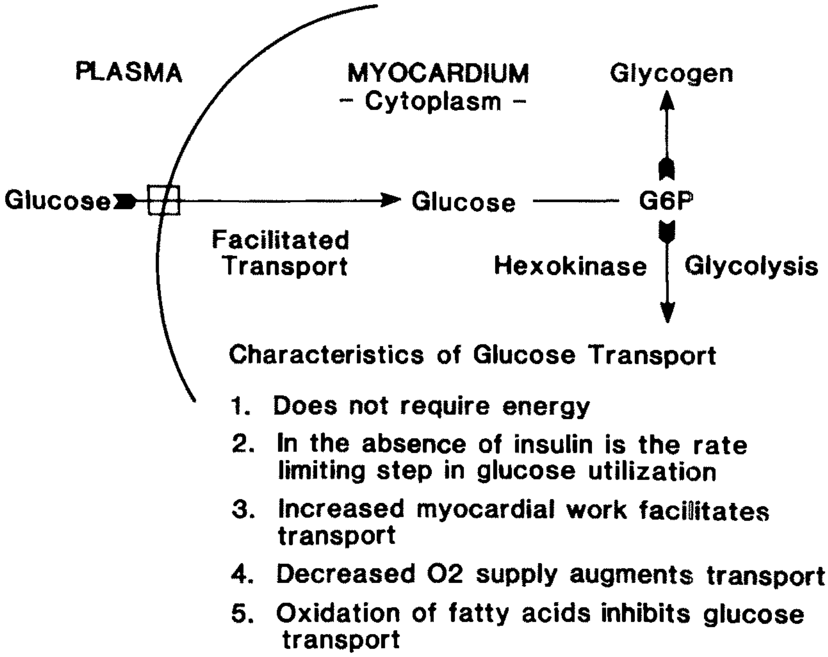


Figure 1. Fuel metabolism in the normal heart is illustrated, as are the two primary pathways for energy generation (glucose and fat metabolism). Oxidation of fat may take any one of three forms: endogenous stores, circulating FFAs, and circulating triglycerides. The primary circulating fuel is FFAs, even though triglycerides are present in plasma. Glucose can be obtained from circulating glucose or myocardial glycogen stores. Of note is that lactate can travel bidirectionally. It is produced under anaerobic conditions and released from the myocardium. Under aerobic conditions, when it is present in high concentration in plasma, the myocardium may oxidize lactate as a primary energy source. (From Askanazi J, et al: Nutrition and cardiac function. *In* Kaplan J (ed): Cardiac Anesthesia, Edition 2. Philadelphia, Grune & Strattton, 1987; with permission.)

and ketones may all, under different circumstances, play a role in fuel metabolism. Glucose metabolism generally occurs along two pathways, glycolysis and oxidative phosphorylation. The latter includes the citric acid cycle and the electron transport system. Glycolysis produces a small amount of ATP compared with oxidative phosphorylation (Fig. 2); since it can proceed anaerobically, however, it becomes significant during anoxic and hypoxic conditions. Fatty acids are metabolized aerobically, and therefore, use somewhat more oxygen per kcal of energy generated than does glucose.

***Relation Between Glucose and Fatty Acid Utilization and Oxidation.*** In 1963, Randall et al put forward a comprehensive scheme, called the glucose fatty acid cycle, to explain the interrelation between rates of glucose and fatty oxidation in muscle.[180] Various lines of evidence support the hypothesis that fatty acid reduces glucose oxidation in vivo and in



**Characteristics of Glucose Transport**

1. Does not require energy
2. In the absence of insulin is the rate limiting step in glucose utilization
3. Increased myocardial work facilitates transport
4. Decreased O2 supply augments transport
5. Oxidation of fatty acids inhibits glucose transport

Figure 2. Characteristics of glucose transport. (From Askanazi J, et al: Nutrition and cardiac function. *In* Kaplan J (ed): Cardiac Anesthesia, Edition 2. Philadelphia, Grune & Stratton, 1987; with permission.)

vitro.[134] These can be summarized as follows: (1) oxidation of fatty acids by perfused preparations of both heart and skeletal muscle causes inhibition of glucose utilization and oxidation; (2) in vivo studies demonstrate that the artificial raising of blood fatty acid concentration markedly reduces whole body glucose utilization and oxidation; (3) administration of nicotinic acid in man will lower the blood fatty acid concentration and increase the rate of glucose utilization; and (4) under conditions at which glucose utilization is known to be reduced in the intact animal (diabetes), the blood fatty acid concentration is elevated and lipid oxidation is enhanced.

### Fuel Utilization in the Myocardium

Cardiac muscle is capable of using a wide variety of substrates as sources of energy.[14,114,143] Although glucose and plasma free fatty acids are the primary fuels, lactate, pyruvate, ketone bodies, triglycerides (both circulating and stored in the myocardium), and to a lesser extent amino acids, can all serve as sources of energy under varying conditions. It should be emphasized that plasma free fatty acids, circulating triglycerides (the primary form of circulating fat), and endogenous fat stores are all metabolized differently and must be considered separately. Utilization of these substrates by the heart is a function of (1) concentration of the substrate in plasma, (2) availability of alternate competing substrates, (3) mechanical activity of the heart, (4) supply of oxygen, and (5) plasma levels of certain hormones. It is important to remember that the oxygen supply may be varied by the content of oxygen in the blood (that is, hypoxia) as well as the blood flow (ischemia). It should be emphasized that hypoxia and ischemia are distinctly different conditions that have markedly different effects on substrate utilization by the heart. As we will see, a number of controversies have developed over the use of glucose-insulin-potassium therapy in hypoxia and ischemia; in many respects, these controversies can be related to the condition being treated and the parameters under examination.

Mitochondria make up about 35 per cent of the total volume of cardiac muscle.[172] Under normal circumstances, oxidative phosphorylation accounts for almost all of the ATP produced. In a well-oxygenated heart all of the substrates are completely oxidized in the citric acid cycle. Glycolysis is an important source of ATP only when oxidative metabolism is compromised. The importance of fatty acids in myocardial metabolism is well known. Their oxidation under some conditions may account for as much as 100 per cent of oxidative phosphorylation.[115,116,125,135,231] Under most conditions free fatty acids are utilized in preference to carbohydrate; their oxidation normally accounts for 60 to 70 per cent of oxidative metabolism. This is particularly true at high levels of cardiac work where fatty acids are the main substrate utilized.[35,130] In studies of the isolated perfused myocardium, when free fatty acids were not included in the perfusate, glucose oxidation was observed at low and high cardiac work levels. At the low work rate, glucose oxidation accounted for only 40 per cent of the oxygen consumption; at the high work rate, on the other hand, glucose oxidation accounted for as much as 80 per cent of the total oxygen consumed. This shows that lipid is the preferred fuel at low work rates, although glucose was used in preference to endogenous stores of lipid at the high work rate. This should not, however, be taken to imply that circulating plasma free fatty acids would not be a preferred energy source in the whole body, even at high work rates. The normally low rate of carbohydrate utilization can also be increased several fold when oxidative metabolism is reduced.[131] The acceleration and alterations of substrate utilization under various conditions involves a complicated system of regulatory interactions in various metabolic pathways, the glucose fatty acid cycle.[134,180] These interactions bring about the integrated control of substrate utilization and adjust rates to match substrate supply with energy needs.

### Regulation of Carbohydrate Utilization

Although fatty acids appear to be the preferred fuel under most circumstances, glucose represents an important fuel for respiration in aerobic hearts. Its metabolism through glycolysis is a major source of ATP in hypoxic tissue. The major steps in glucose utilization are believed to be regulated by glucose transport, hexokinase, phosphofructokinase, pyruvate dehydrogenase, as well as glycogen synthetase and phosphorylase. The pathways of glucose and glycogen utilization are illustrated in Figure 1.

Transfer of glucose across the cell membrane occurs by a process known as carrier-mediated transport of facilitated diffusion[148] (Fig. 2). In this system the mobile protein component (the carrier) moves through the membrane and is fairly accessible to glucose on either side. Free glucose combines with the carrier on one side of the membrane, rendering the sugar complex sufficiently lipid soluble to allow it to pass through the membrane. The complex then dissociates, releasing free glucose on the opposite side of the membrane. The process is freely reversible. It does not use metabolic energy and serves only to equilibrate intracellular and extracellular concentrations of glucose. In the absence of insulin, glucose transport is a rate-limiting step for glucose utilization by heart muscle.[121,149] Under this condition, phosphorylation of glucose by hexokinase is limited by the low concentration of intracellular free glucose. If transport in isolated rat hearts is stimulated by insulin, free glucose accumulates in the cell and the rate-limiting step in glucose utilization is shifted from transport to the hexokinase reaction.[173]

Sugar transport in heart muscle is accelerated by a number of factors in addition to insulin. Increased work accelerates the rate of glucose utilization, and stimulation of transport has been demonstrated to be a primary component of this effect.[130] When transport is augmented, glucose utilization in the myocardium is inhibited by the presence of high circulating levels of alternate substrates such as free fatty acids or ketone bodies, partly through the consequent inhibition of glucose transport. Oxidation of fatty acids will inhibit glucose transport when transport has been stimulated by either insulin or increased cardiac work. A decrease in oxidative metabolism accelerates glucose transport in the heart. The presence of palmitate does not inhibit transport in anaerobic hearts, which suggests that the fatty acid must be oxidized before transport is inhibited. Thus, glucose transport is regulated by insulin, cardiac work, availability of alternative substrates (which apparently must be oxidized to have an effect), and the degree of oxygenation of the heart.

Intracellular free glucose is phosphorylated to glucose-6-phosphate before it can be metabolized further. Phosphorylation is catalyzed by the enzyme hexokinase. In in vitro studies, hexokinase is inhibited by glucose-6-phosphate.[34] Thus, when glucose-6-phosphate accumulates intracellularly, the negative feedback of hexokinase acts to decrease its continued production. Glucose-6-phosphate is the first branch point in glucose metabolism; it may be converted to pyruvate through the glycolytic pathway, converted to glycogen, or enter the pentose phosphate cycle.

Control of the glycolytic pathway occurs primarily through the activity of phosphofructokinase and pyruvate dehydrogenase. Phosphofructokinase catalyzes the first irreversible step in glycolysis and its activity controls the overall rate of this pathway under many conditions.[120,179] The enzyme is subject to allosteric regulation by a variety of small molecules. Its activity is inhibited by ATP and citrate, and accelerated by free phosphate, fructose diphosphate, ADP, and cyclic AMP.[7,61,108,161,166,167] Phosphofructokinase is one of the major sites of glycolytic inhibition by aerobic respiration. In well-oxygenated hearts, when tissue levels of ATP are high, phosphofructokinase is inhibited.[136,181] Inhibition of glycolysis by oxidation of fatty acid at both high and low levels of ventricular pressure development involve high tissue levels of citrate and ATP, both of which inhibit phosphofructokinase.[132] When oxidative metabolism in muscle is limited, phosphofructokinase is activated by decreased levels of ATP and increased levels of free phosphate.[41,232] Increased cardiac work accelerates the activity of this enzyme[132] by an unknown mechanism.

The conversion of pyruvate to acetyl-CoA in the mitochondria is catalyzed by pyruvate dehydrogenase. This is the second important regulatory step, after the phosphofructokinase reaction, in glucose oxidation. Pyruvate dehydrogenase is inhibited by the products of pyruvate oxidation, NADH, acetyl-CoA, and ATP.[41,232] Oxidation of fatty acids results in inhibition of pyruvate dehydrogenase due to increased levels of NADH and acetyl-CoA.

### The Effect of Increased Cardiac Work on Glucose Utilization

Provision of both palmitate and glucose to hearts developing higher levels of ventricular pressure results in preferential use of fatty acids.[130] In perfused hearts, in the absence of insulin, with buffer containing glucose as the only substrate, the rate of glucose utilization was increased when the beating hearts increased the peak systolic pressure.[131] These data indicate that over 95 per cent of the maximum rate of glucose utilization by isolated hearts could be controlled by metabolic factors due to ventricular pressure development. This effect of pressure development is involved in acceleration of sugar transport as well as an activation of phosphofructokinase.[132]

Addition of palmitate to the perfusate inhibited the stimulated rate of glucose utilization at the higher work loads, but failed to further reduce the slow rate of utilization at low work loads. Inhibition of glucose uptake at the higher levels of ventricular pressure development involved decreased rates of both transport and flux through the phosphofructokinase reaction. Increased pressure development accelerated the rate of glycogen utilization in hearts perfused with glucose as the only exogenous substrate. This effect was prevented by including either insulin or palmitate in the perfusate. Thus, increased cardiac work has a dual effect on glucose transport. It directly stimulates glucose oxidation and also renders the tissue more sensitive to stimulation by insulin.

## Effects of Ischemia and Hypoxia on Myocardial Metabolism

Metabolism of the heart during ischemia and hypoxia is characterized by a decreased rate of ATP production from oxidative phosphorylation and an increased rate of glycolysis. The rate of synthesis of acetyl-CoA from both pyruvate and beta oxidation of fatty acids is reduced by anoxia and the tissue levels of acetyl-CoA and the citric acid cycle intermediates decrease. Fatty acids are diverted from beta oxidation to deposition as tissue triglycerides and pyruvate is diverted to formation of lactate.[56,123,124] In both hypoxic and ischemic hearts, the initial limiting factor in ATP production is reduced oxygen supply and decreased oxidative phosphorylation. In addition to oxidative phosphorylation, ATP can be produced by substrate level phosphorylation in the glycolytic pathway and at the succinate-thiokinase reaction in the citric acid cycle. Fumarate-dependent oxidation of NADH has been reported to contribute to ATP production in anoxic hearts that were perfused with buffer containing fumarate.[33] Evidence of the relative contribution of the mitochondrial reactions to anaerobic ATP production in the absence of exogenous citric acid cycle intermediates is not available. The rate of glycolytic ATP production is increased five-fold by anoxia in isolated rat hearts; however, this increased rate of glycolysis was not sufficient to maintain normal tissue concentrations of high energy phosphate. Estimates of glycolytic contribution to anaerobic ATP production ranged from 10 to 30 per cent of total energy requirements.

It should be emphasized that a lack of $O_2$ leading to low ATP levels is not the only condition that occurs during ischemia. After 1 minute of ischemia left ventricular function deteriorates while ATP is still normal.[33] Progressive fall in ATP over time occurs during ischemia; after 12 minutes there is still 75 per cent of control levels of ATP while left ventricular function has completely deteriorated.[129]

The increased rate of glycolysis that occurs in the early phase of ischemia is not maintained with continued exposure to decreased oxygen supply.[10] The metabolic alterations that occur during the early transition from aerobic to anaerobic metabolism involve activation of carbohydrate utilization at the levels of glucose transport, hexokinase, and phosphofructokinase. Factors in glycolytic reactions that limit glycolysis after 2 to 3 minutes of anoxia are not fully understood. In the absence of insulin, glucose transport appears to be a rate limiting step. When insulin is added to the perfusate, intracellular free glucose accumulates, suggesting that an effect on glycolysis is the limiting factor. It has been suggested that phosphofructokinase may be limited due to a greater inhibitory effect of ATP at a pH below neutrality.[169] Thus, with increased levels of lactate, flux through glycolysis may result in a decreased pH. Although glycolysis can produce only limited amounts of ATP, the beneficial effects of glycolysis in hypoxic hearts are well documented. The rate of beating in anoxic rat hearts is maintained longer when glucose is available[119]; glucose loading in the in situ dog heart before anoxia improved postanoxic recovery[12,27]; high levels of glucose helped prevent morphologic changes in the mitochondria of anoxic rat hearts.[67] Experimentally, in the isolated perfused heart, ischemia and hypoxia result in differing reponses. In general, hypoxia accelerates consumption of glucose to a greater extent than ischemia. This may be due to a greater accumulation of metabolites with ischemia than with hypoxia.

When the normal dog heart was given a choice between lactate, glucose, or fat, lactate was the preferred substrate.[47] Figure 3 demonstrates that with increasing arterial concentration of lactate (up to 4.5 mmol per L) there is continued extraction by the heart for energy utilization.[47] This occurs in the presence of high concentrations of glucose and free fatty acids. Experimentally, the extraction rate plateaus at a point when arterial lactate exceeds 4.5 mmol per L. At this point, lactate supplies almost 90 per cent of myocardial energy needs. During exercise, lactate may account for up to 60 per cent of myocardial $O_2$ consumption.

Glycogen breakdown may also contribute to the flow of glucose through glycolysis during anoxia. The progressive fall in cardiac glycogen

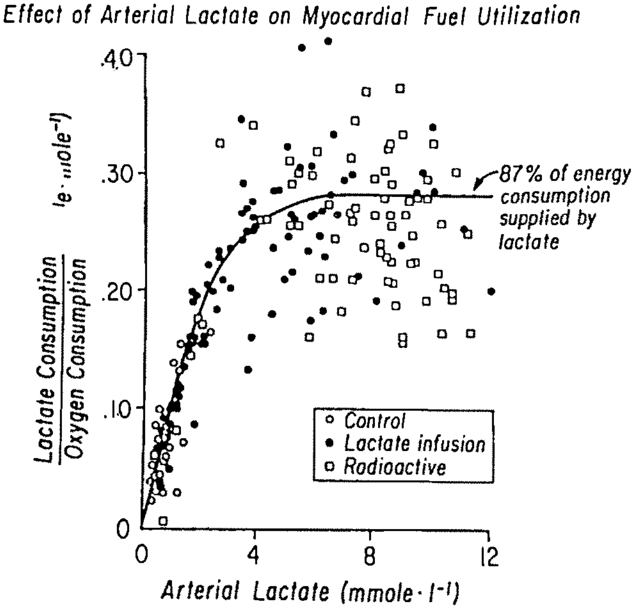


Figure 3. Uptake of lactate as a function of arterial concentration. (From Drake AJ, et al: Preferential uptake of lactate by the normal myocardium in dogs. Cardiovasc Res 14:65–72, 1980; with permission.)

levels in the early neonatal period appears increasingly related to resistance to anoxia.[229] Nevertheless, the increased rate of transport of glucose, mobilization of glycogen, and activation of phosphofructokinase in oxygen deficient states was not enough to maintain the tissue level of ATP. Within 1 minute the level of creatinine phosphate decreased 30 per cent, while within 2 minutes ATP decreased by 25 per cent. It should be noted that ventricular failure can occur in hearts while the level of intracellular ATP is still high suggesting that (1) much of the ATP may not be available for contraction; and (2) the contractile process is inhibited. In general, ventricular failure occurs when ATP decreases by 25 per cent.

### Control of Myocardial Lipid Utilization

Fatty acids have a number of effects on cardiac metabolism and function. As discussed earlier, fatty acids are oxidized in preference to carbohydrate and represent a major source of fuel for myocardial energy production. The tissue levels of high energy phosphates are kept at a higher level in hearts perfused with free fatty acids as compared with glucose. However, it should be noted that high levels of free fatty acids have several detrimental effects on myocardial function. Very high concentrations of free fatty acids increased the rate of myocardial $O_2$ consumption; in ischemic heart patients, high plasma free fatty acids are associated with the development of cardiac arrhythmias.[31,128] In isolated rat hearts and in the dog heart, abnormally high concentrations of free fatty acids result in decreased force of muscle contraction and development of arrhythmias.[20,75,142,209]

### Plasma Free Fatty Acid Metabolism

Plasma free fatty acids are the primary source of fat for oxidation in the myocardium. Free fatty acids are not soluble and bind to albumin.[65] Fatty acid extraction by tissues is thought to occur at cellular binding sites, competing with the binding sites on plasma albumin. Cellular uptake of free fatty acids has been shown to depend on the albumin to free fatty acid molar ratio.[55] Since the physiologic concentration of albumin in the serum does not vary extensively, uptake under most conditions is proportional to the concentration of plasma free fatty acids. Fatty acids can be supplied to the heart from plasma triglycerides or lipoproteins. However, these form only a small part of that used for fat oxidation in the myocardium.

Fatty acids taken up by the heart are activated within the cytosol by formation of fatty acyl-CoA, and transferred to the site of beta oxidation (mitochondria) by a carnitine-dependent process. It is apparent that, in some instances, the availability of carnitine may be a limiting factor in oxidation of long chain fatty acids. Thus, carnitine supplementation has been observed to be of use in conditions where there are increased myocardial fuel requirements.

### Integrated Control of Fatty Acid Utilization

The overall rate of fatty acid utilization is determined by (1) the supply of exogenous free fatty acids, (2) the energy demands for the heart, and (3) transport of free fatty acids into the mitochondrial matrix by the carnitine-dependent pathway. At a constant rate of energy utilization, increased supply of fatty acids has only a limited ability to accelerate fatty acid uptake. The upper limit is reached when the supply of fatty acids exceeds the capacity of the cells to bind free fatty acids and to convert the acyl units to

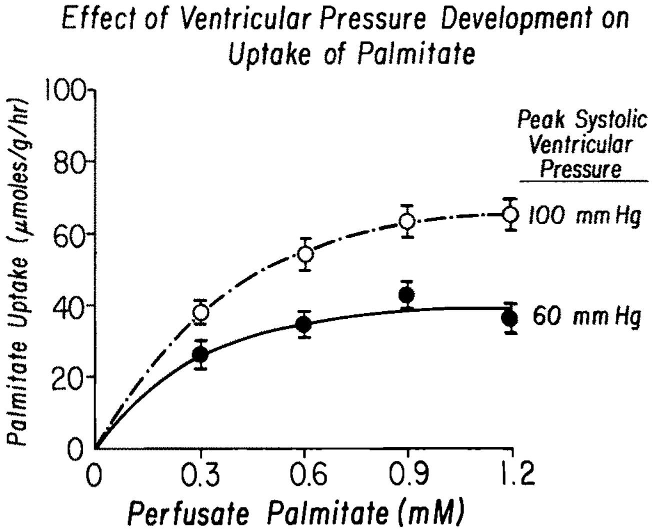


Figure 4. Changes in ATP and creatine phosphate (CP) during ischemia. Following 12 minutes of ischemia, ATP levels are still 75 per cent of control level. (From Neely JR, et al: Myocardial utilization of carbohydrate and lipids. Prog Cardiovasc Dis 15:289, 1972; with permission.)

$CO_2$, complex lipids, or metabolic intermediates. At any constant level of fatty acids, increased cardiac work will increase fatty acid utilization (Fig. 4).

Increased cardiac work accelerates the rate of fatty acid uptake at all concentrations studied. This accelerated rate results from an increased rate of oxidative phosphorylation and a greater than two-fold increase in the rate of oxygen consumption. The rate of oxygen consumption is also increased in hearts oxidizing fatty acids as compared with those oxidizing glucose.

## Fat Metabolism During Oxygen Deficiency

With a decrease in oxygen supply, oxidation of fatty acids by the heart sharply declines.[56,143] Fatty acid uptake may continue but a large fraction is converted to serum lipids. Other than the inability to synthesize ATP, the consequences of reduced fatty acid oxidation is not known. The presence of high levels of fatty acids may decrease myocardial contractility[74] and increase arrhythmias.[155] High levels of free fatty acids have also been reported to be uncouplers of oxidative phosphorylation and to increase myocardial oxygen consumption.[30] Under experimental conditions, however, the increase in $O_2$ consumption equals only the theoretical increase expected from a shift from glucose to fat oxidation.[144]

In the resting state, fatty acids are the predominant source of energy for the heart, with glucose and lactate serving as lesser fuel sources. Glucose utilization is regulated by free fatty acids, which inhibit glucose transport into the cell.[175] Glucose may either be used to synthesize glycogen, or via glycolysis, metabolized to pyruvate. When the heart is well perfused pyruvate is directed through the Kreb cycle, resulting in ATP production. In physiologic states in which acidosis and increased levels of NADH exist, such as in ischemia and shock, pyruvate is metabolized to lactate.[122] Increased lactate decreases fatty acid oxidation by inhibiting carnitine acyl-

CoA transferase I, the enzyme responsible for the incorporation of free fatty acids into cell mitochondria.[13] Ischemia and hypoxia, per se, but not necessarily lactate and acidosis, decrease beta oxidation, the metabolism of long chain fatty acids into two carbon fragments.[122]

Although our knowledge of the metabolic effects of septic shock on the human heart is limited, canine studies have shown that endotoxin infusion results in increased utilization of lactate over free fatty acids.[213] As mentioned previously, lactate infusion causes a direct decrease in free fatty acid metabolism in dogs.[214]

Endotoxin infusion has been shown to be associated with an increase in myocardial ATP,[165] which is postulated to be due inhibition of Na-K ATPase.[103,105,141]

The effects of sepsis and high serum lactate levels on myocardial metabolism seems to include increased lactate metabolism, decreased free fatty acid uptake into mitochondria and decreased beta oxidation, decreased glucose metabolism, increased shunting of pyruvate to lactate and a possible increase in myocardial ATP.

More research is required regarding the role of the endogenous fuel sources postulated by Dhainaut,[45] and the effect of septic shock on myocardial metabolism in humans in general.

## PULMONARY CIRCULATION, RIGHT VENTRICLE, AND RESPIRATORY PUMP

While the existance of left ventricular dysfunction, documented by either decreased LVSWI, diminished response of LV performance to volume loading, or decreased LVEF has been confirmed by several investigators, the existance and significance of right ventricular failure is less well defined. Septic shock is often associated with MSOF and respiratory distress. The mechanical effects of ARDS and PEEP, regional hypoxic vasoconstriction, changing endogenous and exogenous vasoactive millieu, and their effect on right ventricular afterload are difficult to separate from the primary effect of sepsis on right ventricle. Furthermore, the right ventricle may be more technically difficult to visualize and techniques to image the right ventricle are relatively new. Therefore, information regarding RV function during septic shock is less clear compared with studies of LV function.

Pulmonary vascular endothelium is frequently injured in sepsis with resulting changes in metabolism, vasomotion, and permeability. All three factors may affect pulmonary circulation and right ventricular afterload.

Clowes[32] noted elevation of RV pressures, suggestive of pulmonary hypertension, in 6 of 10 patients with peritonitis. They postulated that pulmonary hypertension plays a part in the development of right ventricular failure, and that it occurred at a time when hypoxemia was present.

Zapol[227] and Zimmerman[228] and others have shown that pulmonary hypertension is commonly seen in severe ARDS and may be associated with reduced right ventricular stroke work index (RVSWI). Many investigators[111,204,205,207] have shown that moderately severe pulmonary hypertension in patients with ARDS reduces RVEF and increases RVEDV. Right ventricular subendocardial hypoperfusion may be a factor in the setting of hypotension and severe pulmonary hypertension.

Sibbald et al[203] studied 37 patients with sepsis. They noted that 22 of 37 patients had a PAD-PAOP gradient of greater than 5 mm Hg and concluded that these patients had a much greater likelihood of death (83 per cent) within 48 hours than those without evidence of hypertension. The finding that active early pulmonary vasoconstriction is a negative prognostic indicator has been reproduced by others.[110]

Hoffman et al[79] performed RV nuclear ejection fractions on patients resuscitated from hypovolemic septic shock. The majority of patients displayed decreased RVEFs. Patients in this study who displayed both decreased LVEF and RVEF (5 of 16) had an 80 per cent mortality.

Kimchi[92] found depressed RVEF in 52 per cent of patients with septic shock; 62 per cent of these were associated with depressed LVEF. RVEF did not correlate with standard hemodynamics or the presence of respiratory failure. Contributions of increased right ventricular afterload or depressed contractility were not separated.

Parker[160] also provided evidence that depressed RVEF is associated with depressed LVEF; both improved in survivors within 10 days.

It may be concluded that some element of RV dysfunction probably occurs in some patients with septic shock independent of respiratory failure. Clinical evidence of acute RV failure is rare in previously well patients with septic shock, however, RV dysfunction may exist without the clinical manifestations of acute RV failure.[202] RV dysfunction in association with LV dysfunction, due to global depression of contractility rather than ventricular interdependence, may predict a poor prognosis even though pulmonary hypertension seems to influence reversibility. More work is required before the exact role of RV dysfunction in the pathogensis of septic shock is elucidated.

The pulmonary pump has received considerable attention lately. Sepsis is usually accompanied by multifactoral tachyapnea; endogenous stress hormones, lactate, reduction in cerebral blood flow, and acute changes in pulmonary flow and pressure may be involved. Acute early mortality in sepsis may be related to the failure of respiratory pump before damage to gas exchange units occurs. Oxygen cost of breathing may increase ten-fold, and in situations of fixed $DO_2$, respiratory muscle fatigue may occur within a few hours.

In a canine model of low cardiac output shock, Aubier[11] has shown that shock increases respiratory muscle work, increases respiratory muscle lactate production, and decreases respiratory muscle glycogen. Intubation and mechanical ventilation reduced mortality due to electromechanical dissociation of diaphragm and reversed the derangement in respiratory muscle lactate production and glycogen depletion. Vires has shown in a canine model of low output shock, the induction of shock increases the percent of cardiac output to respiratory muscles 70 per cent (from 3 to 21 per cent of total $DAO_2$). Concomitantly, flow to liver, brain, and skeletal muscle were decreased. Mechanical ventilation prevented this shunting of blood to respiratory muscles, increased flow to liver and brain, and decreased serum lactate levels.[223]

Although this description is derived from canine experiments of low flow shock, the deversion of flow to respiratory muscles, the increased lactate production, and decreased glycogen stores may explain in part the mixed metabolic/lactic acidosis and respiratory hypercapnic respiratory failure seen in patients with septic shock with low output state.

The issue of respiratory muscle perfusion and function was addressed by Hussain[81-85] in a series of experiments in a canine model of hypodynamic acute sepsis. Initial observations pointed out that death occurred due to respiratory arrest resulting from respiratory muscle fatigue manifested by deteriorating inspiratory flow rate and transdiaphragmatic pressures in the face increased electrical output, normal lung mechanics, and oxygenation. Mechanical ventilatory support reduced respiratory muscle blood flow and diverted oxygenated blood flow to brain and gut in addition to reducing lactic acidosis. Subsequent work showed some six-fold increase in diaphragmatic blood flow and oxygen extraction associated with dramatic increase in diaphragmatic glycogen depletion and lactate production. It was hypothesized that lactic acid and microvascular shunting were synergistic. Nonventilatory therapeutic interventions directed at restoration of blood pressure were studied. Volume resuscitation restored cardiac output and was associated with decreased $DVO_2$ achieved by increased diaphragmatic blood flow and reduced diaphragmatic oxygen extraction. Interestingly, pressor support of norepinephrine did not improve cardiac output; $DVO_2$ was reduced due to increased diaphragmatic oxygen extraction.

Catecholamines seem to have a direct effect on diaphragmatic contractility.

## MANAGEMENT

### Fluids

The use of crystalloid versus colloid in volume resuscitation and maintenance in sepsis is still somewhat controversial but colloid resuscitation seems to improve survival associated physiologic variables more efficiently. Early effect on oxygen metabolism is primarily determined by the presence or absence of oxygen debt.

It is important to realize that the bulk of fluids administered to critically ill patients, after the initial volume resuscitation, consist of nutritional solutions. Nutrients are de facto pharmacologic agents, as discussed elsewhere in this volume, with detectable physiologic effects. Amino acids may increase left ventricular contractility and compliance; their respiratory effects include stimulation of respiratory drive, response to hypoxia and hypercapnea, in addition to their global thermogenetic effect. Rapid infusion of lipids may worsen ischemia and tacharrhythmias; the respiratory effects include reduced respiratory quotient (RQ), and dose dependent pulmonary vascular effects. Glucose loading seems to have beneficial effect on ventricular function; the respiratory effects include increased RQ and response to hypoxia.

Aggressive use of dialytic techniques (continues arteriovenous hemofiltration, untrafiltration, etc.) has been advocated by some investigators in patients with severe sepsis and ARDS but no coherent guidelines exist.

### Ventilatory Support and PEEP

There is a rationale for early intubation and mechanical ventilation in septic patients with persistent lactic acidosis. Since these patients have distributive shock and low preload, increased intrathoracic pressure may reduce cardiac output due to reduction of preload. Prophylactic use of PEEP does not reduce incidence of ARDS. While PEEP does not seem to affect left ventricular systolic function or diastolic compliance per se, it modifies left and right ventricular afterload. Increase in left ventricular output can be seen in patients with severe LV failure and pulmonary edema in the setting of myocardial infarction where the ventricle is more afterload than preload dependent. Further improvement can be produced by the use of cardiac cycle specific increase in intrathoracic pressure by using an ECG synchronized high-frequency jet ventilation.[171] The effect of these techniques in patients with sepsis, depressed LVEF, and variable SVR has not been studied.

PEEP reduces myocardial and diaphragmatic blood flow while renal and cerebral perfusions are not changed. These effects are reversible with volume loading.[46]

### Vasoactive Drugs

While vasoactive drugs are primarily used to optimize perfusion pressure and left ventricular output, they have major indirect effects on regional circulation (renal, mesenteric, coronary vasculature) and ventilation-perfusion relationships (pulmonary vasculature).

Dopamine is usually the primary catecholamine used in septic shock. Its spectrum of activity covers low-dose dopaminergic vasodilatory effect on renal and mesenteric vascular beds, beta adrenergic effects and alpha adrenergic vasoconstriction. Its use may be limited by tachyarrhythmias and worsening hypoxemia due to increase in LVEDP and inhibition of hypoxic vasoconstriction; addition of dobutamine and reduction of the dopamine dose may be useful in these situations and in patients with myocardial depression. Furthermore, the reduction of LVEDP due to increased LV compliance allows for more adequate fluid resuscitation.

Levophed is usually used if the dopamine dose exceeds 10 to 20 $\mu$g per kg per minute. Recent recommendations are to reduce dopamine to dopaminergic range since renal vasodilation can be effectively maintained.[189] Addition of Levophed to high-dose dopamine also seems to be effective, in refractory vasodilated shock, in the terms of elevating SVR and urinary output.[44]

Catecholamines, such as dopamine and dobutamine, increase oxygen consumption in septic shock regardless of the presence of oxygen debt and lactic acidosis. This effect, which may be due to direct modification in oxidative metabolism, may distort our ability to monitor oxygen metabolism.[63] Catecholamines also increase pulmonary shunt but rise in $SVO_2$ and use of PEEP usually prevent clinically significant hypoxemia.

Early use of vasodilators for improvement of LV compliance, facilitation of further volume expansion and reduction in capillary leak has been advocated but not proven to effect survival. Deterioration in oxygenation and borderline blood pressure usually preclude their frequent use in patients with pulmonary hypertension.

## SUMMARY

We have reviewed some of the issues relevant to understanding the cardiovascular physiologic derangement most commonly seen with MSOF, which is septic shock.

The standard pulmonary artery catheter derived hemodynamics are useful. The evolution of physiology in survivors of sepsis seems to follow a predictable pattern. Preshock ability to mobilize $DO_2$, $VO_2$, and CI is followed in the acute 24-hour decompensation phase by the ability to reduce heart rate and increase CI and peripheral vascular tone. Further information is provided by volume, rather than pressure-flow oriented monitoring. Both systolic and diastolic left ventricular dysfunction are evident early in sepsis and a uniform inadequate response to volume challenge has been documented. Survivors manifest acute reversible cardiac dilation and reduction in ejection fraction. Overall, the majority of patients who expire due to sepsis demonstrate reduced ventricular compliance, tachycardia, and refractory peripheral vasodilation resulting in persistent shock or rapidly progressive MSOF. Less than a third of mortalities are associated with hypodynamic state.

Considerable information is available as to regional circulation and metabolic function. The global oxygen metabolism demonstrates pathologic dependence of oxygen consumption and oxygen delivery; this seems to hold for vital organ systems. Myocardium shows profound coronary vasodilation and shift in substrate utilization to lactate. The possibility of endogenous myocardial substrate utilization exists with unclear implications as to cardiac function or relationship to circulating levels of myocardial depressant substances. Respiratory muscle blood flow and oxygen consumption increase drastically and can be beneficially modified by standard therapeutic interventions.

Vasoactive drugs have predictable effects on oxygen metabolism and regional circulations. Their selective use can beneficially affect diastolic compliance, gas exchange, renal blood flow, and the ability to provide adequate fluid resuscitation. Positive pressure ventilation, PEEP, and nutritional infusions produce predictable hemodynamic changes that are frequently not considered in the assessment of patients in septic shock.

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# Hemorrhagic Shock

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Several sources of circulatory collapse can lead to hypotension, poor tissue perfusion, and, finally, the shock syndrome. The leading etiologies of shock are hypovolemia, heart failure, and sepsis[37,40]; of these, the most common is hypovolemia. The loss of blood (through external or internal bleeding) or plasma (through peritonitis, burns, or crush injury) leads to situations in which the effective circulatory fluid volume (ECFV) (which is in dynamic equilibrium between plasma, interstitial and intracellular spaces) is diminished, causing inadequate cardiac output because of a decreased red cell mass or ECFV depletion.[40,46]

This article will be devoted to a discussion of hemorrhagic shock, one of the major aspects of hypovolemic shock. We will begin with current hypotheses as to the pathophysiology of hemorrhagic shock, then its sequelae on different organ systems will be discussed briefly, as will the use of parenteral nutrition in the late stages of hemorrhagic shock. The bulk of this review will focus on the most important treatment modality—volume resuscitation.

## PATHOPHYSIOLOGY

Despite recent progress in hemodynamic monitoring, circulatory assist devices, ventilatory support, the development of new antibiotics, and aggressive supportive therapy that includes blood products, total parenteral nutrition (TPN), cathecholamine support, and new intravenous fluids, mortality from cardiogenic shock remains at 85 to 90 per cent,[24] and mortality from septic shock is still 40 to 90 per cent.[61]

In contrast, mortality from hemorrhagic shock or the development of late multisystem organ failure depends primarily on how quickly underlying problems can be identified and treated appropriately. Once multisystem organ failure develops, increased mortality rates ensue; when more than three systems are involved, the mortality rate is more than 90 per cent, despite maximal support.

ECFV loss can be compensated, up to a certain point, before shock

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develops. For example, a healthy 70-kg man can lose 1000 ml of blood without serious complications (Table 1).

The initial compensatory neurohumoral reaction (baroreceptor discharge triggered, resulting in the release of catecholamines with their vasoconstrictive, inotropic, and chronotropic effects) maintains an adequate oxygen supply to the heart and brain. The heart rate and contractility increase, whereas filling pressures of the left and right ventricles may decrease. Blood flow is redistributed to vital organs at the expense of alpha receptor-rich organs (kidney, mesentery, muscle), and systemic vascular resistance increases.

To restore the ECFV, normal blood-tissue exchange is disrupted to provide transcapillary fluid homeostasis. Pituitary adrenocorticotropic hormone (ACTH), antidiuretic hormone, and aldosterone secretion occur in response to the reduction in blood volume. Fluid is mobilized from extravascular spaces (interstitial, intracellular) to refill the plasma compartment while hematocrit values are falling.

Hyperglycemia, which develops in response to increased levels of catecholamines, is an important mechanism in the redistribution of ECFV. Glucose remains in the extracellular fluid spaces and draws fluid by osmotic pressure from extravascular to vascular spaces.[29,30] Friedman and colleagues[22] showed a strong correlation between glucose levels and the hematocrit, indicating that blood glucose may be a determinant in plasma refill.

However, if there is no compensation for fluid loss because of the continuing presence of a causative factor or because of inadequate treatment, pulmonary gas exchange will deteriorate as a result of an imbalance between ventilation and perfusion in the lungs, and oxygen saturation of arterial blood will decrease. If the oxygen insufficiency is localized by the mechanism described, only the peripheral organ will suffer. If the oxygen debt is present in a vital organ, however, shock will be manifested profoundly. Shoemaker and associates[71] have shown that a decrease in oxygen consump-

**Table 1.** *The Response to Various Degrees of Hemorrhage in Humans*

| BLOOD LOSS | VASCULAR RESPONSE | METABOLIC RESPONSE | SIGNS AND SYMPTOMS |
|---|---|---|---|
| Minimal (15%) | Recruitment of ECF: contraction great veins | Slight | Transient |
| Moderate (30%) | Arteriolar constriction, reduced flow to skin, bone, and muscle; tachycardia, reduced cardiac output | Increased glycolysis and lipolysis; increased glucose, fatty acids, lactate in blood; ventilatory alkalosis; decreased urinary sodium and volume | Thirst, orthostatic hypotension, apprehension, weakness, and pallor |
| Severe (42%) | Cardiac output markedly reduced; hypotension; blood flow to viscera impaired | Severe lactic acidosis; severe oliguria; mixed venous $PO_2$ approaching 20 mm Hg | Air hunger, altered state of consciousness |

*From* Trunkey DD, Sheldon GF, Collins JA: The treatment of shock. *In* The Management of Trauma, Edition 3. Philadelphia, WB Saunders Company, 1979, p 80.

tion ($VO_2$) will occur in the early "ebb" stage of shock or even before the initial hypotensive event.

Uncorrected blood volume loss of more than 40 per cent will rapidly result in cellular anoxia. The aerobic citric acid cycle malfunctions, and the pyruvate-lactate shunt becomes the primary pathway for the generation of adenosine triphosphate (ATP). As the energy supply drops below 60 per cent, the sodium-potassium pump activity deteriorates, and cellular edema develops.[14,68] At this point, swelling and degeneration of the cell can be reversed,[11] but with time ischemia develops, leading to many irreversible changes and loss of function.

Ventilation-perfusion inbalance in hemorrhage is initially manifested as an increase in physiologic dead space. Oxygen delivery, which is normally approximately 1000 ml per minute, decreases dramatically with the subsequent impairment of peripheral oxygenation, leading to cell membrane changes. Because of the lack of oxygen, the aerobic Krebs cycle cannot be maintained, resulting in overproduction of anaerobic lactic acid. This leads to a direct myocardial depressant effect with resulting poor response to endogenous and exogenous cathecholamines. It is also possible that a myocardial depressant factor is present.[44,60]

Persistent acidosis, associated with hypoperfusion, impairs the sphincter tone of precapillary arteriolar sphincters while postcapillary sphincters remain closed. When capillaries do not function as an exchange system, blood pools in the peripheral circulation and is unable to return to the heart because of persistent venous constriction. At this stage, shock is refractory (stagnant).[65]

The fact that shock may become irreversible has been explained by the concept of vicious cycles or "the domino effect,"[21] when shock may become endotoxic because of absorption of endotoxin from the intestine or rapidly developing multisystem failure.

The longer the state of shock persists, the less it is responsive to treatment. The removal of metabolic products from the periphery is insufficient; metabolic acidosis remains and becomes more profound, producing hyperventilation with an increase, finally, in arterial $PCO_2$; cell mitochondrial structures become damaged and lysosomal membranes rupture. Circulating lysomal enzymes and products of lysomal hydrolases induce vascular permeability, pulmonary and heart damage, and production of myocardial depressant factor.[45] Various systems and cascades are activated in the shock state, released by hypoxic or anoxic cells.

The primary goal of shock therapy is to treat the condition correctly and as early as possible so as to prevent the sequelae of late shock. Vigorous volume replacement and restoration of perfusion pressure are specific goals of therapy.

## SHOCK AND INDIVIDUAL ORGAN SYSTEMS

### Heart

The immediate effect of hemorrhagic shock is on the circulation, so the heart is immediately affected because of the disproportion between the demand and supply of oxygen, particularly when coronary artery disease is present. The myocardium has the highest resting oxygen extraction rate (70 to 75 per cent),[23,36] and even with the effect of autoregulation coronary artery flow suffers, especially with tachycardia and shortening of the diastolic time interval. Coronary blood flow becomes pressure dependent in the face of ineffective autoregulation; it becomes the determinant of myocardial oxygen and metabolic requirements in a system with an extremely high extraction ratio. The decrease of coronary blood flow leads to a myocardial anaerobic metabolism and depletion of glycogen stores. Myocardial contractility diminishes, causing an increase in left ventricular filling pressure. This leads, in turn, to a decline in subendocardial flow and precipitates ischemia. Systemic oxygen extraction increases with falling cardiac output. When the arteriovenous oxygen difference is more than tripled and cardiac output at rest falls to less than one third of its normal value, the inevitable result is circulatory collapse and death.[26] Early shock is characterized by low preload, low cardiac output, and increased systemic vascular resistance. Inadequate volume replacement or late treatment will result in increased preload with low cardiac output and increased systemic vascular resistance; at this stage a release of a myocardial band of creatine kinase resulting from myocardial damage is observed, and pump failure may develop.

### Lungs

The effect of bleeding on pulmonary function is complex. Respiratory failure may develop suddenly as shock results in increased work and oxygen cost of breathing due to hyperventilation in the face of reduced oxygen availability.[15] In prolonged shock, hypoventilation, due to respiratory muscle fatigue, and eventual failure may be seen.[3] Animal models of acute, severe hemorrhage (50 per cent blood volume loss) do not provide evidence of early microvascular injury; prolonged shock resulted in increased permeability in 30 per cent of subjects.[18] Rapid, multiple blood transfusions have been implicated in the development of adult respiratory distress syndrome (ARDS).[38] Microembolic complications may be present with impaired lung function and could be one of the causes of single- or multisystem organ failure. Fibrin and the fibrinolytic system may be responsible for increased vascular permeability and pulmonary edema.[12]

ARDS may develop because of multiple mechanisms, or it could be manifested as a complication of a single-system failure and post-traumatic pulmonary insufficiency.

In analyzing the duration of untreated hemorrhage in combat casualties, Collins[15] confirmed that the ventilatory response to shock becomes blunted with increased duration of the shock.

### Liver

The liver, one of the main regulatory organs, is often involved and damaged by hemorrhage and hypotension to a much greater extent than is commonly realized.

De la Monte and coworkers,[17] who analyzed autopsied livers from patients with a history of one or more episodes of hypotension several days before death, observed midzonal hepatic necrosis in 18 of these livers and suspected that this pattern might be associated with the shock. In clinicopathologic studies of 15 cases of massive hepatic necrosis after shock, Irie and Mori[39] observed, for the most part, a centrilobular liver necrosis pattern due to shock of various causes. It is well known that there is a relationship between shock and disseminated intravascular coagulation (DIC) that promotes formation of fibrin thrombi in the microcirculation and increases tissue hypoxia. Release of transaminases (serum glutamic oxaloacetic transaminase [SGOT] and serum glutamic pyruvate transaminase [SGPT]) into the bloodstream and failure of the liver to detoxify waste products can lead to irreversible shock. In addition, in profound hypotension, shock could develop in the liver within minutes, rather than in 1 hour, as suggested by Carlson and Lefer[10] after their experiments with cats' livers.

Chaudry and Baue[13] showed that the metabolic capacity of hepatic mitochondria decreases with shock, and they also indicated that intravenous infusions of epinephrine (in doses usually used in shock therapy) decrease hepatic transmembrane potential. Therefore, epinephrine could be responsible for hepatic depolarization during hemorrhagic shock.

### Gastrointestinal Tract

Gastrointestinal failure resulting from hemorrhage and sequential mucosal ischemia may be observed as erosive mucosal lesions (petechiae, ulcerations) that occur initially in the stomach and duodenum but can be demonstrated throughout the gastrointestinal tract; with prolonged shock, the tract could become necrotic, with major bleeding from these lesions. Several reports indicate that the normal intestinal barrier is affected by hypovolemic shock, and with impaired mucosa, bacterial endotoxins cross the intestinal membrane, are absorbed by peritoneum, and rapidly produce septic shock.[65]

Ischemia in the pancreas can cause early pulmonary failure,[5] producing free fatty acids, phospholipase A, and other toxic substances that are damaging to alveolar capillary membranes. Myocardial depressant factor, which could precipitate the shock, seems to originate in the pancreas.[45]

### Kidneys

One of the major complications of shock with prolonged hypotension is renal failure. Renal blood flow changes are greater in the outer cortical area (because of increases in vascular resistance) when compared with the juxtamedullary and the medullary areas of the kidney.[43] High renin levels (as a response to hemorrhage) contribute to vasoconstriction and probably increase ischemic injuries. Increased free water absorption is seen with elevations in antidiuretic hormone. Progressive azotemia may develop with or without oliguria. High-output renal failure may be observed. Therefore, early diagnosis and treatment are important and can prevent the development of prerenal azotemia or its progression to acute tubular necrosis.

### Brain

Multiple studies indicate that cerebral perfusion is the best example of autoregulation in the various vascular systems, showing a cerebral flow that is practically constant within a wide range of systemic pressures (50 to 60 to 180 mm Hg).[35,42] Permanent brain damage is to be expected only in uncontrolled, profound, and prolonged hypotension.

## PATIENT ASSESSMENT

### Clinical, Noninvasive Assessment

The patient should be examined for (1) the primary cause of hemorrhage; (2) signs of respiratory failure; (3) pulse, pulse pressure, and systemic blood pressure readings; (4) skin temperature; (5) signs of congestive heart failure; (6) level of consciousness; (7) urine output; and (8) pre-existing heart disease, lung disease, or both. The noninvasive assessment should be very brief. Even a short physical examination will often allow the physician to define the apparent cause of the hemorrhage (for example, a wound or gastrointestinal bleeding). Simultaneously, large-bore intravenous catheters must be inserted and blood samples sent to the laboratory for hematocrit and hemoglobin determinations, glucose, blood urea nitrogen (BUN), creatinine, and electrolyte levels, plus determination of blood type and cross-matching.

The determination of blood lactate is a reliable and sensitive test that correlates very closely with mortality; when the concentration approaches 8 mM per L, the incidence of fatal outcomes reaches 90 per cent.[83]

When using the hematocrit as a test to monitor hemorrhagic shock, one should remember that there is a delay of approximately 2 hours before it reflects a real loss of blood[46]; a reduction in red blood cell mass is accompanied by a lesser depletion in plasma volume, which is defended by interstitial capillary autotransfusion and neurohumoral discharge directed at sodium retention.

Arterial blood gas determinations are a routine, precise test to assess oxygenation and ventilation; they help to manage cardiorespiratory function, to prevent cerebral damage.

### Invasive Assessment

For effective treatment of shock, it is routine in modern intensive care units to employ the following means of invasive assessment:

***Central Venous Pressure (CVP) Catheter.*** A CVP catheter allows measurement of right ventricular filling. Unfortunately, CVP is not necessarily an accurate guide for assessing the severity of a patient's condition or blood volume deficit. Because of the body's compensatory mechanisms, venous pressure could be normal despite large volume loss; if the patient has been given venoconstrictive pressors, the venous pressure could be higher than normal. It is also inaccurate as an indicator in the presence of single- or biventricular heart failure, myocardial infarction, or lung disease.

Changes in CVP in response to fluid load are probably a more reliable indicator than is a single measurement of CVP. In patients who do not respond to fluid resuscitation, the insertion of a Swan-Ganz catheter is advised for more accurate assessment and management.

***Arterial Line.*** It is preferable to insert a central (femoral, axillary) arterial line because of the likelihood of peripheral vasoconstriction. Under these conditions, a central arterial line will also make it easier to take the multiple blood samples required by the high intensity of treatment.

***Foley Catheter.*** This catheter is used to monitor hourly urine output, urine sodium levels, and urine osmolarity.

***Swan-Ganz Catheter.*** This catheter is a useful diagnostic tool in severe hemorrhagic shock. It provides important information about left ventricular filling pressure, permits samples to be taken for the measurement of arteriovenous oxygen difference, and allows the assessment of cardiac output by thermodilution or the Fick method. In addition, it is very useful for optimal intravenous fluid management once inotropic support has been started and when the patient is on positive pressure ventilation with positive end-expiratory pressure (PEEP).

Conversely, one must remember that the interpretation of data obtained with a Swan-Ganz catheter can at times be very difficult, particularly when influenced by the condition of the lung parenchyma, the intrathoracic pressure, positive pressure ventilators, the presence of anatomic intracardiac shunts, or tricuspid insufficiency.

A decision based only on data gathered from the Swan-Ganz catheter, ignoring the patient's dynamic physical examination, may sometimes lead to mistakes.

Although we do not advocate the use of the Swan-Ganz catheter in each patient with significant hemorrhage, we nevertheless feel that at present this is the best way to manage the patient who is suffering from shock and has underlying cardiopulmonary disease, a high CVP, persistent lactic acidosis, and pulmonary edema.

The monitoring goals of therapy[72] are systolic blood pressure $>100$ mm Hg, diastolic blood pressure $>50$ mm Hg, urine output $>30$ ml per hour, urine sodium level $>20$ mEq per L, hematocrit 30 to 40 per cent, $P_vO_2 \geq 30$ mm Hg, PCWP $<15$ mm Hg.

Measurements of oxygen metabolism are the most sensitive and specific of the monitored variables for acute circulatory failure.[72] Oxygen delivery, mixed venous oxygen ($P_vO_2$), and anion gap are very important data for assessing the patient in shock.

## TREATMENT OF SHOCK AND MULTIPLE SYSTEM FAILURE

### GENERAL PRINCIPLES

The first priorities in treatment are airway assessment, oxygenation, and provision of adequate ventilation using a nasal cannula, Venturi mask, or intubation, if necessary, to keep the $PO_2$ at approximately 70 mm Hg and the $PCO_2$ at approximately 25 to 30 mm Hg. The next step is to restore the ECFV to an adequate level and ensure that cardiac function is sufficient. Next, monitor urine output and look for the underlying problem. After this, gastrointestinal tract injury must be prevented (nasogastric tube and antacids to keep gastric pH above 5.

### TOTAL PARENTERAL NUTRITION

Specific nutritional support of patients in shock is now considered a useful and important clinical tool. In the early stages of shock, glycogenolysis continues in the liver until its stores are depleted. Because skeletal muscle is a major storage site for glycogen in the body, the cessation of glycogenolysis in muscle limits the availability of carbohydrate fuels. Protein use is significantly elevated, and mobilization of free fatty acids is decreased after the suppression of oxidation.

In prolonged shock, hyperglycemia and lactic acidemia decrease in response to the rapid mobilization of carbohydrate stores. Metabolic muscular failure resulting from a deficit of branched-chain amino acids in the muscles may be observed.[9]

A number of other problems may be observed with protein calorie malnutrition, including difficulties in ventilation, loss of muscle strength, and so on. This state is characterized by increased amino acid metabolism, primarily of the essential branched-chain amino acids, in spite of the high plasma concentration of energy substrates.[33]

The current approach to nutritional therapy includes administration of increased amounts of protein (up to 2 to 3 gm per kg) and increased branched-chain amino acid concentrations (not yet available commercially). A moderate amount of carbohydrate calories should be given to meet obligatory glucose requirements, but glucose administration should be tempered with the knowledge that hypertonic glucose dosages are usually ineffective in these patients and could precipitate increases in oxygen consumption, carbon dioxide production, and norepinephrine excretion.[2]

## RESUSCITATION IN HEMORRHAGIC SHOCK

### Fluids for Volume Alone

***Crystalloids.*** The first step in the resuscitation of the patient in hemorrhagic shock is to restore the circulating blood volume. Exactly how best to accomplish this seemingly simple goal has been the subject of much controversy over at least the past 25 years.

*Isotonic Solutions.* The importance of the interstitium in the resuscitation of hemorrhagic shock has been known since the work of Shires and associates in the early 1960s.[68,69] It was this work that led to the increased use of crystalloid solutions, particularly Ringer's lactate. The proponents of crystalloid resuscitation have cited the following reasons for their preference:

1. Crystalloid solutions cost less, even though greater volumes must be used when compared with colloid solutions.
2. Multiple physiologic abnormalities were found in subjects after resuscitation when albumin-containing solutions were used.[16,47,49,58,81]

In recent years, another fear has developed, the risk of viral disease transmission, primarily acquired immunodeficiency syndrome (AIDS), through the use of human blood component products.

Isotonic crystalloids have been used successfully to resuscitate the victims of acute hemorrhagic shock. Ringer's lactate is currently the fluid of choice for resuscitation of hypovolemic trauma victims.[1] It is usually administered in a ratio of 3 ml of crystalloid per milliliter of shed blood.

*Hypertonic Solutions.* The use of hypertonic crystalloid solutions has also been suggested for resuscitation of the hemorrhagic shock victim. Monafo has successfully used such solutions for burn resuscitation for many years.[56,57] These solutions appear to act by osmotically removing intracellular water (because the sodium is actively kept out of the cell) and replenishing the extracellular (interstitial and then intravascular) space.

Velasco and associates[79] showed that dogs could be resuscitated from hypovolemic shock using small amounts of hypertonic saline. Traverso and coworkers[76] showed that hypertonic sodium chloride solutions were effective in restoring hemodynamic stability after nonlethal hemorrhage in swine. Survival after lethal hemorrhage was improved when 7.5 per cent sodium chloride was used (as compared with 0.9, 5.0, or 10.0 per cent sodium chloride) to replace 25 per cent of shed blood volume. Peters and associates,[62] using hypertonic Ringer's lactate solution, resuscitated swine in hemorrhagic shock to physiologic end points (defined as a return in cardiac output to a control level while limiting pulmonary wedge pressure to within 3 mm Hg of the control). They showed that although both the standard and the hypertonic Ringer's lactate solutions could restore hemodynamic "normalcy," the volume required was less and the mean arterial pressure was higher with the hypertonic solution.

In a study performed in patients undergoing elective aortic aneurysmectomy, Auler and associates[4] infused equal volumes (4 ml per kg) of isotonic and hypertonic (7.5 per cent) saline solutions immediately after aortic unclamping. Whole blood and Ringer's lactate were used intraoperatively to maintain cardiac output and pulmonary wedge pressures at near preoperative levels. During the first 24 hours postoperatively, Ringer's lactate was used as needed to maintain left atrial filling pressures at normal levels. The recipients of the hypertonic saline had higher pulmonary wedge pressures and cardiac indexes and lower systemic and pulmonary vascular resistance, and they required less volume transfusion.

Bitterman and coworkers,[6] using both cats and rats, showed a hemodynamically significant but transitory response to 7.5 per cent saline infusion (4 ml per kg) after hemorrhagic shock. When shed blood was reinfused, the hemodynamic values in the animals treated with hypertonic saline were significantly higher than those observed in the animals treated with normal saline.

Because response to hypertonic saline seems to be good but transient, the question arises of whether hypertonic saline mixed with a colloidal solution would be better. Kramer and associates[41] resuscitated sheep with a 200-ml bolus of hypertonic (7.5 per cent) saline mixed with 6 per cent dextran 70 or 200 ml of normal saline to simulate field resuscitation of trauma victims. The sheep were then observed for 30 minutes without any further fluid administration (to simulate the time it takes to transport the victim), and then both groups were given Ringer's lactate as needed to restore or maintain cardiac output baseline values for the next 2 hours. After the 200-ml infusion, the animals in the hypertonic group had normal cardiac output and blood pressure. These values remained normal for the 30-minute observation period. Urine output and oxygen consumption were actually higher than baseline values in this group during this period. At the conclusion of the additional 2 hours of observation, the sheep receiving the hypertonic solution had required only one sixth of the Ringer's lactate used for the animals receiving the normal saline bolus.

A more direct comparison of normal saline, hypertonic saline, dextran 70, and the combination of hypertonic saline and dextran 70 was made by Maningas' group.[51] Although that study also used fixed volumes and not physiologic end points, it was a better comparison among hypertonic saline, dextran 70, and the combination of the two. After hemorrhagic shock was induced, resuscitation (with a volume equal to 25 per cent of the shed blood) was accomplished with normal saline, hypertonic saline (7.5 per cent sodium chloride), 6 per cent dextran 70, or a combination of hypertonic saline and dextran. Survival rates were 100 per cent with the hypertonic saline and dextran solution, 69 per cent with 6 per cent dextran, 53 per cent with hypertonic saline, and 13 per cent with normal saline.

In human trauma victims, Modig[54] compared resuscitation with physiologic end points (blood pressure >100 mm Hg, CVP >6, and urine output >60 ml per hour) using Ringer's acetate or a combination of dextran 70 and Ringer's acetate, both groups receiving whole blood as needed to keep the hematocrit between 30 and 33 per cent. Not only did the hemodynamic features normalize faster in the group receiving dextran, but that group also had a significantly lower incidence of ARDS (0 of 14 versus 5 of 17).

***Colloids.*** *Colloids with Protein.* For acute volume resuscitation, the use of albumin solutions has decreased and the use of Ringer's lactate solution has increased since the late 1960s. This has occurred despite the fact that colloids have some theoretic and practical advantages: (1) less overall volume is required, potentially leading to faster resuscitation times, and (2) there is less tissue edema (primarily pulmonary edema).[19,31,34]

Initially, human serum albumin, usually in a 5 per cent solution, was used for colloid resuscitation. Today the use of heat-treated human albumin is minimal, and the use of fresh frozen plasma seems to be increasing. This is more likely due to the fact that fresh frozen plasma contains clotting factors rather than to the fact that it has significant oncotic activity. The primary disadvantages include a minimum 20-minute delay from the time it is requested until it is available, the high cost of processing blood into fresh frozen plasma, the limited availability of a human blood product, and its potential, albeit small, to transmit viral disease. Despite these drawbacks, studies continue to evaluate its efficacy in resuscitation.

Traverso's group[77] compared resuscitation in swine with whole blood, untyped porcine fresh frozen plasma, compatible porcine fresh frozen plasma, 5 per cent human albumin, and normal saline. The model was shown to be 100 per cent lethal without resuscitation. Shed blood was replaced in a 1:1 ratio with each of the preceding solutions. Survival was highest in the whole blood group, followed closely by the compatible fresh frozen plasma group. These groups were not statistically different. Both, however, had statistically higher survival than the other groups. (Several early deaths were seen in the porcine fresh frozen plasma group. These were attributed to compatibility problems.) Also, both whole blood and fresh frozen plasma were better acid buffers than were human albumin or normal saline. In another study, Lucas and colleagues[48] showed that the addition of fresh frozen plasma to a resuscitation regimen of packed red blood cells and balanced electrolyte solution led to higher cardiac output, left ventricular stroke work, and pulmonary capillary wedge pressure.

*Colloids Without Protein (Dextran and Hetastarch).* The dextran solution most often used, dextran 70, is a solution of polymerized glucose molecules with a mean molecular weight of 70,000. Its use was discussed previously in the section on hypertonic solutions.

Another colloid solution that has been used in resuscitation is hetastarch. In its 6 per cent concentration, it exerts essentially the same oncotic pressure as a 6 per cent protein solution.[18] As a manufactured product, its availability is high and its cost is low when compared with human blood products. Problems arise when large volumes are infused because the coagulation mechanism may be impaired. Maximum dosage is limited to 1500 ml per day or 20 ml per kg, according to the package insert. Hetastarch may be interchangeable with dextran, but further investigative work needs to be done as the experience with dextran is greater.

## Fluids for Oxygen Delivery and Volume

***Blood.*** Although crystalloids and colloids can restore circulation, living tissues need oxygen in order to function effectively. Oxygen delivery depends on several factors, including cardiac output, hemoglobin concentration, hemoglobin saturation, and, to a much lesser extent, arterial oxygen tension. The most effective, and until recently the only, oxygen-carrying compound was hemoglobin in the red blood cell. Each gram of hemoglobin can combine with approximately 1.34 ml of oxygen. Assuming a saturation of almost 100 per cent and a normal hemoglobin concentration of 15 gm per dl, this would yield almost 20.1 ml oxygen per dl blood. Compare that with the amount of oxygen dissolved in the plasma, which is directly proportional to the partial pressure of oxygen ($PO_2$) in the blood. (The plasma content of oxygen = $PaO_2 \times 0.0031$ ml per dl. In the best circumstances with room air, $PaO_2$ is approximately 100 mm Hg, so plasma oxygen content is 0.31 ml per dl, or about 1/70 that of hemoglobin.)

The best source of hemoglobin is the red blood cell. With the modern technology available to separate whole blood into its component parts and the shortage of blood donors, whole blood is virtually unavailable for resuscitation. Instead, packed red blood cells are the current standard.

***Red Blood Cell Substitutes.*** *Fluosol-DA.* To reduce dependence on human blood products, much research has been done to find a substitute for the oxygen-carrying capability of the red blood cell. Stroma-free hemoglobin and the perfluorochemical compounds come to mind. The most well known of the latter is Fluosol-DA, a combination of perfluorodecalin and perfluorotripropylamine. High hopes have been held for this compound in the resuscitation of trauma victims and for those refusing blood transfusions because of religious beliefs. Gould and associates[25] showed that in patients suffering from "severe" acute anemia who refused blood transfusions, Fluosol-DA was ineffective in providing sufficient oxygen-carrying capability. In their patients, Fluosol-DA carried only about one half of the oxygen that plasma did. As can be seen by the preceding example, this is about 1/140 of what normal blood (hemoglobin) can carry. In Gould's study, in a severely anemic individual Fluosol-DA delivered about 0.7 ml per dl of oxygen at a $PaO_2$ of 430 mm Hg and a "fluorocrit" (volume of Fluosol-DA/volume of blood) of 5 per cent. Six patients received Fluosol-DA only and eventually died. A seventh patient received Fluosol-DA only and lived. The eighth patient received packed red blood cells in addition to Fluosol-DA and survived. Therefore, only one of seven patients who received just Fluosol-DA survived. (All patients without "severe" anemia survived without the Fluosol-DA.) It is possible that if the severely anemic patients had received more Fluosol-DA, more of them might have survived. Yet they had already received the maximum dose of the drug allowed by the Food and Drug Administration (FDA). Alternatively, work by Ohyanagi and Saitoh[59] clearly showed that when administered to patients with "severe" anemia Fluosol-DA carried up to 20 per cent of the oxygen that hemoglobin did and up to 150 per cent of the oxygen that plasma carried. The difference between these two experiments is in the definition of "severe" anemia, thus leading to some confusion as to the more valid study. Gould's group defined severe anemia as a hemoglobin concentration of no more than 3.5 gm per dl or an oxygen extraction ratio of no less than 50 per cent, whereas Ohyanagi and Saitoh did not specifically define it, although it appears to be, on the average, a hemoglobin concentration less than 10 gm per dl, almost three times greater than Gould's definition of severe anemia.

## Other Pharmacologic Resuscitative Aids

***Catecholamines.*** Catecholamines have traditionally been used to maintain blood pressure in hypotensive situations. For the individual in hypovolemic shock, it is now well recognized that catecholamines should be used only when "the pump is primed," that is, after there has been adequate volume resuscitation of the victim. The key to resuscitation is restoration of normal cellular function, initiated by restoring cellular perfusion and oxygenation, not by maintenance of an arbitrary blood pressure.

***Steroids.*** There has been much controversy over the use of steroids in shock (primarily septic shock). Recently, Hardaway and colleagues[32] infused pigs with hemolyzed red blood cells, which is known to cause DIC, and then subjected them to hypovolemic shock. Half of the pigs received methylprednisolone, 30 mg per kg, just prior to administration of the hemolyzed red blood cells. These swine experienced less of a prolongation in prothrombin time and partial thromboplastin time and less of a decrease in fibrinogen levels and platelet counts, leading the authors to conclude that steroids protect against DIC. Administration of the steroids before the shock insult invalidates these results when applied to trauma victims, who rarely inject themselves with pharmacologic doses of steroids prior to sustaining major trauma.

Alternatively, two well-designed studies, the Methylprednisolone Severe Sepsis Study Group[8] and the Veterans Administration Systemic Sepsis Cooperative Study Group,[80] both showed that the administration of pharmacologic doses of steroids did not alter survival in patients with sepsis. In fact, the latter study showed that there was no significant difference in DIC occurrence between the steroid-treated group and the nonsteroid-treated group. These studies were performed in septic patients and experimentally have little bearing on patients with hypovolemic shock. Work of this quality needs to be repeated in studies on patients in hypovolemic shock.

According to Sharpe and Chernow, steroid therapy is not useful in the treatment of hemorrhagic shock.[66]

***Arachidonic Acid Metabolites.*** *Prostaglandins and Prostaglandin Inhibitors.* Elevated levels of prostaglandins $PGE_1$, $PGF_{2\text{-}\alpha}$, and $PGA_1$ have been found in animals in hypovolemic shock. Additionally, treatment with prostaglandin inhibitors has been shown to improve certain parameters related to hypovolemic shock. Alternatively, administration of certain prostaglandins ($PGE_1$, $PGE_2$, $PGF_{2\text{-}\alpha}$) has been shown to increase survival in experimental hypovolemic shock.[50,83]

*Prostacyclin, Thromboxanes, and Thromboxane Antagonists.* Prostacyclin ($PGI_2$) is a vasodilator and is the most potent platelet antiaggregator known, whereas thromboxane $A_2$ is a vasoconstrictor and the most potent platelet aggregator known.[63] Both are derived from the endoperoxide $PGH_2$. Their half-lives are very short (3 minutes and 30 seconds, respectively), and their activity is measured by assaying their stable metabolites rather than the active compounds themselves. The relative actions of these "opposing" arachidonic acid metabolites is an area of great interest.

Thromboxane antagonists are also under study. Bitterman and coworkers[7] showed that infusion of the thromboxane receptor antagonist BM-13505 into cats that were hemorrhaged resulted in significantly higher mean arterial blood pressures and superior mesenteric artery flow than that in controls after shed blood was reinfused.

*Leukotrienes.* The end products of the 5-lipoxygenase pathway, leukotrienes, are important cell mediators. 5-Lipoxygenase is found in platelets, white blood cells, and lung tissue. $LTC_4$, $LTD_4$, and $LTE_4$ are collectively known as the slow-reacting substance of anaphylaxis (SRS-A); $LTB_4$ is a powerful chemoattractant, whereas $LTA_4$ apparently has no biologic activity. It must be recognized, however, that the exact role of these arachidonic acid metabolites in shock has not yet been elucidated.

***Endorphins and Opiate Antagonists.*** Endorphins are endogenous opiates whose activities are poorly understood. Experimental work has been done in hemorrhagic shock, showing a beneficial effect when beta-endorphin receptors are blockaded with naloxone.[28,52,54,75] Involved were improvements in mean arterial blood pressure, cardiac output, stroke volume, left ventricular contractility, total peripheral resistance, and survival in several species. These results now need confirmation in human beings.

*Thyrotropin Releasing Hormone.* Thyrotropin releasing hormone (TRH) has been studied as an antagonist to endogenous opiates in the treatment of many types of shock.[53] Sugiura and colleagues[73] demonstrated improved survival after TRH treatment in dogs subjected to hemorrhagic shock when compared with controls (9 of 10 versus 5 of 11). The TRH-treated dogs also had higher mean arterial pressure, cardiac index, stroke index, right and left ventricular stroke work indexes, and arterial pH during the uncompensated shock period than did the control dogs.

Gurll and associates[27] compared monkeys and dogs treated with TRH and found that although in the primates TRH improved survival and increased mean arterial pressure and left ventricular $dp/dt_{max}$, when compared with controls, there was no hemodynamic effect or increase in survival in the dogs.

Another study showing the beneficial actions of TRH administration in canine hemorrhagic shock was performed by Teba and associates,[74] who showed that mean arterial pressure, cardiac output, and systemic vascular resistance were significantly improved in the dogs treated with TRH when compared with controls. Also, oxygen delivery, but not oxygen consumption, was increased in the TRH-treated animals.

## CORRECTION OF COAGULATION DEFECTS

In the trauma victim, ongoing bleeding is the most common "coagulopathy." Assuming appropriate mechanical hemostasis, the dilution of intrinsic clotting factors, including platelets, is the usual reason for ongoing bleeding. Platelet transfusions should be considered first when bleeding is persistent. Then, the administration of fresh frozen plasma, which, as already mentioned, contains all the normal clotting factors, should be considered. DIC is not an uncommon finding in the trauma patient. Recalling that hemorrhage and massive transfusion are not the only causes of DIC in the trauma victim, DIC is best treated by first eliminating its cause and then replacing the missing clotting factors.

## RESUSCITATION IN PRACTICE—RECOMMENDATIONS

The most commonly used fluid for acute volume resuscitation continues to be an isotonic solution, either Ringer's lactate solution or normal saline (0.9 per cent sodium chloride). According to current experimental work, it appears that hypertonic saline solutions (7.5 per cent sodium chloride), perhaps mixed with 6 per cent dextran 70, may be the fluids of choice in the future.

Until more work is done in the area of hemoglobin or red blood cell substitutes, only the real thing—packed red blood cells, should be used to improve oxygen-carrying capability. Fluosol-DA, and its associated compounds, should be used at present only in experimental protocols or perhaps for patients who refuse, on religious grounds, to receive human blood products.

Because of its limited availability, fresh frozen plasma should be used only for clotting factor replacement and not for initial volume resuscitation.

Steroids should not be used in the acute resuscitation of the trauma victim.

The biochemical adjuncts to resuscitation, including prostaglandins, thromboxanes, leukotrienes, opiate inhibitors, and TRH, are experimental at best. Significantly more work, including appropriate human studies, needs to be done before their use can be recommended.

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# Pulmonary Dysfunction in Multisystem Organ Failure

*Greg Ruskin, MD,* and Harry Ulrich, MD†*

Pulmonary dysfunction in the patient with shock and multisystem organ failure may take the form of parenchymal injury culminating in the adult respiratory distress syndrome (ARDS), or abnormalities of respiratory muscle function and central drive, which result in pump failure. The clinical importance of respiratory muscle fatigue is reflected by the high incidence of hypercarbic respiratory failure despite "normal" lungs in the patient with shock and metabolic acidosis. In this article, aspects of both parenchymal and nonparenchymal respiratory dysfunction in the patient with shock will be addressed with a focus on issues relevant to patient management.

## RESPIRATORY MUSCLE FAILURE IN SHOCK

In 1981, Aubier et al[11] studied the respiratory response to cardiogenic shock in a canine model of cardiac tamponade. After infusion of saline into the pericardium, a 70 per cent reduction in cardiac output lead to systemic hypotension, lactic acidosis, and a 2 to 3 fold increase in minute ventilation (VE). Animals randomized to receive mechanical ventilation survived the experiment, however, those who continued to breathe spontaneously died after respiratory, not cardiac, arrest. Contractile failure of the inspiratory muscles occurred after a period of anaerobic metabolism and glycogen depletion, which presumably resulted from inadequate energy supply in the face of the increased ventilatory demands imposed by shock. Central respiratory drive as assessed by phrenic nerve activity and diaphragmatic EMG, however, remained intact. In a similar model, it was subsequently shown that during shock, substantial increases in both total and relative respiratory muscle blood flow (RMBF) occurred, the later increasing from 3 per cent to 21 per cent of cardiac output, with a simultaneous reduction in flow to skeletal muscle, liver, and brain. Mechanical ventilation reversed these abnormalities of regional blood flow, and decreased the severity of lactic acidosis by increasing perfusion to nonrespiratory organs and eliminating anaerobic inspiratory work. Since RMBF increased to a far greater extent than would

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be normally required to sustain the modest increase in VE that occurred, contractile failure of the inspiratory muscles implied that shock somehow decreased their efficiency.[10,156]

Respiratory arrest due to inspiratory muscle failure was subsequently demonstrated in an animal model of endotoxic shock. After injection of *Escherichia coli* endotoxin, marked hyperpnea was accompanied by an increase in blood flow to the diaphragm at a time when systemic arterial pressure was falling and flow to nonrespiratory vascular beds was decreasing. Despite increases in respiratory muscle perfusion, anaerobic metabolism occurred at levels of phrenic venous $PO_2$ and diaphragmatic blood flow that would have ordinarily suggested that adequate tissue oxygenation was present. Furthermore, the maximal phrenic arteriovenous oxygen difference ($AVO_2$) was reached before a limitation in perfusion occurred and was significantly less than phrenic $AVO_2$ differences achieved during equal levels of ventilatory stress in nonseptic conditions such as resistance breathing.[79,80,82] These results suggest that endotoxic shock results in the impairment of respiratory muscle oxygen extraction or utilization.

Similar abnormalities of regional blood flow were observed in a canine model of ARDS, where the increase in RMBF was 2 to 3 times greater than that seen in other forms of shock. A simultaneous reduction in flow to splanchnic and renal beds may have been caused by reflex catecholamine release due to hypoxia or the high work of breathing in pulmonary edema.[106]

Although studies comparing the effects of different pressor regimens on respiratory muscle blood flow and energetics are lacking, the administration of dopamine in canine hemorrhagic shock was reported to result in a shift of the pressure-flow curve of the diaphragm, indicating a reduction in flow at any given perfusion pressure.[146] In a model of endotoxic shock, arterial blood pressure was maintained by either volume loading or infusion of norepinephrine, and differences between the two regimens on diaphragmatic blood flow, $AVO_2$ difference, and oxygen consumption were compared. Although diaphragmatic oxygen consumption was equal in both fluid and pressor groups; the animals receiving norepinephrine maintained oxygen consumption at lower levels of perfusion at the expense of augmented oxygen extraction.[81] The infusion of pressors could, therefore, increase the risk of respiratory muscle fatigue if a global limitation of tissue oxygen extraction was present as in severe sepsis. In control animals who remained hypotensive, respiratory muscle efficiency ($VO_2$ per unit work) was significantly less than in those whose blood pressure was maintained with pressors or fluids.

A parallel between the results of these studies and human disease is suggested by the high incidence of paradoxical breathing and subsequent respiratory arrest in patients with shock and metabolic acidosis. Indeed, the most common presentation of septic shock in our intensive care units is acute respiratory failure. Given the high oxygen cost of spontaneous breathing in human shock, optimal respiratory support should be based on modes of ventilation which minimize inspiratory work. The appropriate use of mechanical ventilation may "release" blood flow to critical vascular beds, improve systemic tissue oxygenation, and possibly diminish the risk of multisystem organ failure. Early intubation and mechanical ventilation must be considered in the patient with shock, and weaning should generally be deferred until hemodynamic recovery permits the removal of pressor support. The effects of different forms of shock and pressor regimens on ventilatory pattern, regional blood flow, and optimal type of ventilatory support remain to be determined.

## Abnormalities of Respiratory Drive

The hyperpnea that commonly accompanies shock of diverse etiology is incompletely understood and multifactorial. Metabolic acidosis, endogenous catecholamine release, reflex effects of inflammatory mediators, cerebral ischemia, and hemodynamic abnormalities may all contribute to the ventilatory changes that occur in the absence of overt lung injury or hypoxemia.

Exogenous or endogenous catecholamines such as epinephrine, norepinephrine, and isoproteronol, have long been recognized to stimulate ventilation. "Catecholamine hyperpnea" could result from either direct beta-adrenergic stimulation of peripheral chemoreceptors, or a decrease in baroreceptor and/or chemoreceptor perfusion due to local vasoconstriction. Additionally, the well known calorigenic effects of catecholamines could stimulate ventilation by increasing systemic $CO_2$ production, in which case $PaCO_2$ would be expected to remain normal. Studies in human subjects are limited and conflicting. Keltz et al induced isocapneic hyperpnea in a group of stable asthmatics after intravenous infusion of isoproteronol, which was fully reversed by subsequent beta-blockade.[94] Heisted et al,[75] however, showed that the infusion of norepinephrine or isoproteronol into normal subjects resulted in hypocapneic hyperpnea. Increases in ventilation were out of proportion to changes in oxygen consumption and abolished by beta blockade, suggesting that hyperventilation might be due to stimulation of chemoreceptors.[75] Askanazi[8] recently infused both epinephrine alone or in combination with cortisol and glucagon to normal volunteers, noting increases in ventilation and heightened chemosensitivity to carbon dioxide. Hyperpnea was isocapneic and linearly related to hormonally mediated increases in oxygen consumption. Synergistic increases in both minute ventilation and metabolic rate were found with the combined infusion. This study may be relevant to human hypermetabolic shock, which is associated with increases in these stress hormones.

During normoxia, an isolated reduction of central nervous system (CNS) blood flow may result in a profound stimulation of respiration. Chapman et al demonstrated that progressive cerebral ischemia in anesthetized animals results in isocapneic hyperpnea followed by reversible apnea with more severe ischemia.[32] Beta blockade partially reversed the increases in ventilation and abolished systemic tachycardia, hypertension, and elevated oxygen consumption. The authors speculated that hyperpnea results from a combination of CNS acidosis and adrenergically mediated systemic hypermetabolism. In a similar model, cerebral ischemia was shown to abolish the respiratory compensation to inspiratory flow-resistive loading.[31] Although respiratory arrest occurring in diverse forms of experimental shock has been shown to result from inspiratory muscle fatigue in the presence of intact respiratory drive, it is possible that cerebral hypotension in shock may contribute to early hyperpnea or inadequate responses to mechanical loads such as pulmonary edema.

Isolated hypotension as seen in hemorrhagic shock may cause hyperpnea in the absence of metabolic acidosis due to the effects of secondary catecholamine release or from a primary reduction in carotid sinus blood flow.

In a study of the ventilatory response to acute lactic acidosis, Fulop examined 39 patients with plasma lactate concentrations greater than 7 mmol per L resulting from phenphormin ingestion, sepsis, congestive heart failure, and ethanol intoxication.[58] In most patients, the degree of respiratory compensation was comparable to that seen in other forms of acute or chronic metabolic acidosis; however, patients with coexistent shock had a high incidence of suboptimal compensation as evidenced by a relatively elevated $PaCO_2$. Whether this relative hypercarbia resulted from incomplete or delayed respiratory compensation due to the more rapid onset of acidosis in shock or other factors such as shock-mediated respiratory muscle fatigue could not be determined in this study.

Other factors associated with tachypnea in animal studies that may have some bearing on human disease include isolated increases in pulmonary artery pressure or blood flow, both of which have been associated with increased ventilation. Acute changes in cardiac output cause an immediate increase in minute ventilation, so-called "cardiodynamic hyperpnea," which may result from stimulation of intrapulmonary $CO_2$ receptors.[69] Stimulation of cardiac sympathetic nerves may also result in reflex tachypnea.[179] Inflammatory mediators such as histamine or prostaglandins may stimulate lung irritant receptors, although their role in the tachypnea of early lung injury is purely speculative. Finally, abnormal plasma amino acid profiles in sepsis or hepatic failure may alter CNS amino acid concentrations or their metabolic byproducts, which play a role in the central regulation of respiration.

## PARENCHYMAL DYSFUNCTION

Both direct and indirect injury to the alveolar-capillary membrane from the airway, trauma, or via blood-borne mediators may produce the clinical syndrome ARDS. The term ARDS is somewhat misleading, in that it is not a single disease entity with a specific pathophysiology, but represents a common endpoint of lung injury resulting from a diverse group of clinical disorders. Respiratory failure in septic shock or acid aspiration, for example, may be indistinguishable at the bedside despite clear differences in inciting pathophysiology. The hallmark of ARDS is the presence of increased vascular permeability, which permits pulmonary edema to occur in the presence of normal lung microvascular pressures, as opposed to cardiogenic pulmonary edema, which is the result of elevated hydrostatic pressure. Recent studies have shown, however, that a rigid distinction between these forms of pulmonary edema may be inappropriate, since a significant hydrostatic component may be present in some forms of ARDS. Elevated microvascular pressures may contribute to lung edema, for example, in neurogenic pulmonary edema due to pulmonary hypertension, or in septic ARDS due to endotoxin-mediated venoconstriction. Since the pathology of ARDS is nonspecific, bedside demonstration of increased vascular permeability impractical, and diagnostic serum markers lacking, the diagnosis of ARDS remains a clinical one, and is based on criteria first outlined by Petty over 20 years ago. These include the development of acute respiratory failure characterized by diffuse alveolar-interstitial infiltrates, severe hypoxemia due to shunting, and reduced lung compliance, which usually occur within 72 hours of the precipitating clinical event in the absence of left ventricular failure as a primary cause. Although differentiation between ARDS as defined above and diffuse bacterial pneumonia may be impossible, the problem is moot, since clinical management of both is similar, and no specific therapies for ARDS are available.

Common clinical syndromes associated with a high risk of developing ARDS have been identified in a number of recent studies, including sepsis, massive aspiration, multiple trauma, and hypertransfusion. Isolated bacteremia in the absence of a deleterious systemic response such as hypotension or metabolic acidosis, however, has been shown to carry a relatively low risk of ARDS. Although "shock lung" is a frequent eponym for ARDS, hypotension itself carries a low risk unless accompanied by other factors such as sepsis or multiple trauma. Similarly, multiple transfusion probably does not directly cause lung injury, but serves as a marker for associated risk factors such as trauma. The occurrence of multiple risk factors in a single patient appears to synergistically increase the risk of developing ARDS.[13,52,125,128]

Most of the recent research into the pathophysiology of ARDS has focused on identifying mediators of lung injury generated in the systemic response to sepsis using animal models of lung injury produced by the administration of endotoxin or live bacteria. Although no primary mediator or pathophysiology has been identified, a role for such factors as activated complement, vasoactive arachidonic acid derivatives, and the activated neutrophil has been proposed. The reader is referred to several excellent recent reviews.[17,27,140]

Reported mortality in ARDS has remained relatively unchanged over the past 20 years despite considerable advances in supportive care, and typically exceeds 50 per cent in many recent series,[52,55,125] increasing further in the presence of multisystem organ failure. As pointed out by Rinaldo,[139] however, such statistics may be misleading since patients with more mild disease are frequently excluded in studies using rigid inclusion criteria for ARDS. It is likely that modern intensive care has considerably improved survival in these patients.

## PULMONARY ABNORMALITIES ASSOCIATED WITH SEPSIS

The observation that pulmonary hypertension and hypoxemia are frequently associated with sepsis has been made in clinical studies that have included patients with pulmonary infiltrates and acute respiratory failure, thus making it difficult to assess the pulmonary effects of sepsis in the absence of overt ARDS.[159] Our understanding of the lung's response to peripheral infection is therefore primarily derived from animal models and in vitro preparations. The infusion of endotoxin or live bacteria into a number of animal species typically results in a biphasic response.[27,143] An early phase is characterized by a prompt rise in pulmonary artery pressure, airway resistance, and a decrease in dynamic lung compliance. Additionally, endotoxin has been shown to cause pulmonary venoconstriction and an inhibition of the pressor response to hypoxia.[41,183] An increase in protein-poor pulmonary lymph flow follows these early hemodynamic changes, indicating the presence of hydrostatic pulmonary edema. Early phase hypoxemia occurs in the absence of pulmonary edema, and may result from ventilation-perfusion mismatching due to bronchoconstriction and a loss of hypoxic vasoconstriction. A later more sustained phase is characterized by a reduction, but not elimination, of pulmonary hypertension and the appearance of protein-rich lymph, which indicates the presence of permeability pulmonary edema. It is this later phase that more closely resembles human ARDS. Although the pathophysiology of early and late phase responses are incompletely understood, animal models have suggested that both cyclooxygenase and lipooxygenase products of arachidonic acid may play a major role. Early studies have correlated the appearance of acute phase vascular and airway changes with increased blood levels of prostacyclin and thromboxane metabolites, and demonstrated inhibition of these changes after the administration of cyclooxygenase inhibitors.[166] Recent data suggests that leukotrienes as well may be involved in the mediation of early phase responses, which have been similarly blocked in animals after selective lipoxygenase inhibition. Late phase pulmonary hypertension and increased vascular permeability have also been associated with leukotriene release.[1,27,60]

Similarities between the vasoactive and airway effects of endotoxin in the early phase of animal models and human disease is currently unknown. Neonatal sepsis due to group B *Streptococcus* has been associated with severe pulmonary hypertension, which has been reproduced in an animal model and blocked with a selective thromboxane synthetase inhibitor.[143,175,177] The ability of endotoxin to increase airway resistance in the setting of human ARDS is unknown. Chronic endotoxemia has been shown to result in emphysematous changes, pulmonary hypertension, and muscularization of pulmonary arteries in animal models.[27]

## EFFECT OF HEMODYNAMICS ON LUNG EDEMA AND GAS EXCHANGE IN ARDS

The effects of hemodynamic variables on pulmonary edema formation and oxygenation during conditions of increased pulmonary vascular permeability are complex and incompletely understood. In experimental models, the degree of pulmonary edema may be quantified by measurement of total extravascular lung water (EVLW). In ARDS, unlike cardiogenic pulmonary edema, abnormal vascular permeability results in a direct relationship between EVLW and pulmonary microvascular pressures. Prewitt et al showed that a 4.5 mm decrease in pulmonary capillary wedge pressure (PCW) results in a 50 per cent reduction of EVLW in dogs with acute oleic acid injury.[133] Correlation of hydrostatic pressures with the degree of lung edema may be weak, however, when measured in a mixed population where considerable interpatient variability in vascular permeability and perfused surface area occur.[26]

Recent studies have shown that the site of edema formation in ARDS is not restricted to alveolar capillaries, but includes perialveolar arteries and veins whose contribution to the total amount of fluid filtration may exceed 60 per cent.[2] It is apparent that an increase in the hydrostatic pressure gradient across these vascular channels may result in increased edema formation in the presence of a normal pulmonary capillary wedge or left atrial pressure. This may result from pulmonary venoconstriction due to catecholamines or other vasoactive mediators or pulmonary artery hypertension. Yournes et al recently demonstrated that primary increases in flow in an isolated lobe preparation produced pulmonary artery hypertension and markedly increased EVLW at constant left atrial pressure.[190] At high flow, a reduction in the resistance of vessels proximal (upstream) to sites of fluid filtration occurred in the absence of changes in downstream vascular resistance: this caused the mean hydrostatic filtration pressure to progressively approach pulmonary artery pressure as flow was increased. In a sheep model of endotoxin lung injury, reduction in late phase pulmonary hypertension with nitroprusside decreased EVLW at constant right and left atrial pressures, despite a trend toward higher cardiac outputs.[4] Dauber and Weil[41] demonstrated sympathetically mediated postcapillary venoconstriction in dogs after oleic acid injury by retrograde small vein catheterization. Prevention of the increase in venous pressure at constant LAP with alpha-adrenergic blockade resulted in a 30 per cent reduction in EVLW. The presence of either occult venoconstriction or flow-mediated pulmonary hypertension in ARDS may therefore increase the disparity between the PCW and hydrostatic filtration pressures. In the post-pneumonectomy patient with ARDS and pulmonary artery hypertension, for example, estimated pulmonary capillary pressures may be 20 mm higher than the wedge pressure.

Although in most experimental models of permeability edema increases in cardiac output are accompanied by a rise in PAP, it is likely that an isolated rise in flow is capable of augmenting lung edema formation by increasing the perfused surface area available for filtration. In sheep with permeability edema secondary to microsphere emboli, Obodovitch et al recently demonstrated that an exercise-induced high output state resulted in a significant increase in lung lymph flow at constant LAP and minimally increased PAP.[123] In dogs with oleic acid injury, a rise in cardiac output after the infusion of nitroprusside increased lung edema at constant LAP and PAP. Central venous hypertension may also contribute to edema formation by reducing the pressure gradient favoring lymphatic drainage of the pulmonary interstitium.[3]

Changes in pulmonary flow and/or pressure may have profound effects on oxygenation independent of their effects on lung edema. The end result of a given hemodynamic change depends on the interaction between its effect on shunt, ventilation-perfusion inequality, and mixed venous oxygen tension. A linear relationship between shunt fraction and cardiac output in ARDS has been demonstrated in numerous human and animal studies when flow is varied pharmacologically, mechanically, or indirectly through changes in PEEP.[40,105,163] In experimental ARDS, the rise in shunt fraction after output is increased has been shown to occur in the absence of new edema formation.[24] Diffusion impairment resulting from a decreased transit time was ruled out as a cause of the hypoxemia, which was observed after cardiac output was increased in canine oleic acid injury.[25] A number of animal models have suggested that a redistribution of perfusion to nonventilated lung units occurs as output is increased either by mechanisms of vascular recruitment or by inhibition of hypoxic vasoconstriction. The latter could occur if local pulmonary vasodilitation resulted from a rise in mixed venous oxygen tension ($PVO_2$) that accompanied increasing cardiac output. Although an isolated increase in $PVO_2$ at constant cardiac output was reported to cause a considerable increase in shunt fraction in an animal model of pulmonary edema, the role of venous $PO_2$ in regulating pulmonary vasomotor tone in human ARDS is unknown.[15,144]

It should be remembered, however, that although increases in cardiac output may increase shunt, the net effect on arterial $PO_2$ is quite variable since a secondary rise in $PVO_2$ frequently occurs with augmented flow. This tends to directly improve $PaO_2$ in a lung with significant venous admixture (Fig. 1).

It is, therefore, difficult to predict the effect of administered vasodilators or catecholamines on either shunt or $PaO_2$ in the individual patient with ARDS. Factors such as baseline volume status, pulmonary vasomotor tone, cardiac output, and peripheral oxygen utilization may all modify the response to a given hemodynamic manipulation. The importance of active vasoconstriction in preserving ventilation-perfusion matching in the early phases of ARDS is suggested by the ability of many commonly used vasodilators to worsen oxygenation independently of changes in cardiac output.[14,22,64,65] Melof et al,[111] for example, recently reported that the administration of Diltiazem to a group of patients with ARDS resulted in a 20 per cent increase in shunt fraction and a significant drop in $PaO_2$. A fall in pulmonary artery pressure and vascular resistance after drug administration in the absence of a change in cardiac output implied that changes in oxygenation were due to direct pulmonary vasodilitation.

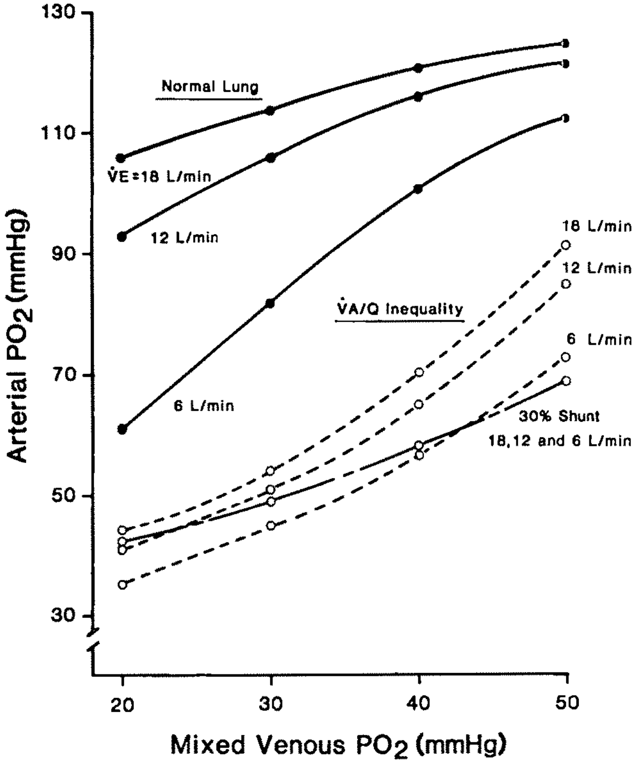

Figure 1. Hypothetical model of the effect of changing mixed venous $PO_2$ on arterial $PO_2$ in a patient with normal lungs, marked V/Q inequality, and a 30 per cent shunt. The effect of a given decrease in venous $PO_2$ on arterial oxygen content is much greater in a lung with significant shunt as opposed to a normal lung due to the shape of the hemoglobin dissociation curve. Increasing minute ventilation is more effective in improving hypoxemia due to venous desaturation in a normal lung as opposed to a lung with significant shunt. (From Dantzker D: The influence of cardiovascular function on gas exchange. Clin Chest Med 4:156, 1983; with permission.)

Similarities between the previously mentioned animal models and human disease may have considerable clinical implications. While a reduction in wedge pressure by diuresis may clearly improve oxygenation, it is also likely that the high cardiac output that commonly accompanies septic ARDS significantly contributes to lung edema formation and hypoxemia, despite its seeming desirability in terms of increasing oxygen transport. Although pharmacologic intervention to lower cardiac output and/or pulmonary artery pressure is theoretically attractive, documentation of the quantitative importance of these variables in the clinical setting is lacking, thus making such therapy experimental at best. Similarly, the potential for vasodilators to worsen oxygenation should restrict their use to the oliguric patient with elevated filling pressures who fails to respond to diuretics or cannot be dialyzed.

## HEMODYNAMIC ABNORMALITIES IN ACUTE LUNG INJURY

Although assessment of the hemodynamic effects of isolated lung injury may be complicated by the presence of superimposed shock, cardiac dysfunction, and exogenous catecholamines, patterns characteristic of ARDS have emerged in clinical studies over the past decade. In 1977, Zapol and associates first reported detailed right heart catheterization data in 30 patients with severe, early ARDS.[192] All had marked elevations in pulmonary vascular resistance (PVR) and PAP which were independent of hypoxia, acidosis, or levels of PEEP up to 30 cm $H_2$. PVR was inversely related to cardiac output for the group as a whole, as well as in individual patients when flow was varied with vasodilators or independently on venoarterial bypass, suggesting that the high PVR in ARDS resulted from either active vasoconstriction or nonfixed anatomic changes. Despite increases in right ventricular afterload and stroke work, cardiac output remained generally normal, progressing to overt pump failure in only a few patients whose mean PAP exceeded 50 mm Hg. Pulmonary hypertension was inversely correlated with both disease severity and mortality. In a retrospective study, Zimmerman et al[194] confirmed the above findings, noting a three- to fourfold increase in PVR, moderate pulmonary hypertension, and normal cardiac output. Pulmonary artery pressure was the only hemodynamic parameter that differentiated survivors from nonsurvivors. Although ventricular volumes were not measured, an elevation of the PCW/LVSW* ratio at high pulmonary artery pressures suggested that left ventricular dysfunction occurred in ARDS, possibly resulting from ventricular interdependence.[194] In both studies, survivors had significant regression of pulmonary circulatory abnormalities with clinical resolution of their respiratory failure. Subsequent studies using either two-dimensional echocardiography or radionuclide angiography in combination with conventional hemodynamic parameters have shown a high incidence of right ventricular dysfunction in ARDS.[86,155,157] Depression of the RVEF, RV dilitation, elevation of RVEDP, and finally abnormal contractility as evidenced by a reduced $PA_{sys}$/RVESVI ratio,* are inversely related to increases in PVR, yet quantitatively minor until the pulmonary artery pressure exceeds a mean of 30 mm.[155] Earlier speculation that ARDS may directly impair left ventricular systolic function has not been supported in these and other studies, however, the elevation of intraluminal LVEDP in relation to echo or radionuclide derived end-diastolic volumes suggest a reduction in LV compliance. Controversy about the presence or magnitude of putative decreases in LV compliance result from the use of intraluminal as opposed to true transmural pressure in constructing LV pressure-volume curves in human studies, and the probable underestimation of transmural pressure in animal studies with the use of esophageal or pleural pressure as an index of juxtacardiac pressure.

The role of coexistent PEEP in producing the increases in PVR, PAP, and RV dysfunction, which are observed in ARDS, has varied considerably in different studies. This is probably due to differing degrees of disease severity, since the effect of a given increase in PEEP on pleural pressure, compression of interstitial vessels, and lung volume is diminished as lung edema increases and compliance falls. Baseline volume status also undoubtedly modifies the effect of a given increment in PEEP on not only ventricular preload, but also on flow-mediated recruitment of the pulmonary vasculature, and hence PVR.

It is important to remember that although measured hemodynamic abnormalities are common, they are infrequently accompanied by a significant reduction in cardiac output, and are therefore of often limited clinical significance. Indeed, many patients with mild ARDS have relatively normal right-sided pressures. Since hemodynamic mortality due to pump failure per se is unusual, the prognostic value of pulmonary artery pressure probably results from its correlation with disease severity. Given the importance of baseline RV function as a determinant of the response to increases in pulmonary vascular resistance, and the frequency of biventricular dilitation and reduced contractility in septic shock, it is often difficult to predict individual hemodynamic responses to lung injury.

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*RVEDP, right ventricular end diastolic pressure; RVESVI, right ventricular stroke volume index; LVSW, left ventricular stroke work.

Hemodynamic effects of vasodilators in patients with early and late ARDS suggest that primary increases in PVR are multifactorial, resulting from both pulmonary vasoconstriction and anatomic derangements. Although the high PVR is both independent of and resistant to oxygen therapy, a role for the presence of pharmacologically mediated active vasoconstriction is suggested by a fall in *both* PAP and PVR after infusion of nitroprusside, isoproterenol, and diltiazem in humans with early ARDS. The relative resistance of the pulmonary circulation to vasodilator-induced reductions in PVR in patients with late disease suggests predominance of fixed anatomic changes.[111,191–193]

Anatomic changes potentially contributing to the increases in PVR include vascular compression due to interstitial fibrosis and edema, as well as intravascular occlusion due to thrombi and smooth muscle proliferation.[70,167] While vasodilators may effect a decrease in PVR and improve parameters of RV function in some patients with early ARDS,[14,158] there is little evidence to suggest that optimization of pulmonary hemodynamics has any bearing on outcome or survival. Additionally, vasodilators may result in a deterioration of oxygenation either through direct inhibition of hypoxic vasoconstriction or indirectly increase shunt fraction by increasing cardiac output. In the occasional patient with life-threatening pulmonary hypertension and right ventricular failure, vasodilator therapy may be used in an effort to reduce PVR and improve RV function, however, these patients generally do poorly due to the presence of irreversible lung injury. There is currently no justification for the routine use of vasodilators to treat the moderate pulmonary hypertension so common in ARDS.

In summary, characteristic hemodynamic abnormalities include a marked early and reversible increase in PVR, mild to moderate pulmonary hypertension, and normal to increased cardiac output. With more severe pulmonary hypertension, RV dilitation and impaired contractility are common, and may be associated with a reduction in diastolic compliance of the left ventricle through mechanisms of interventricular dependence. Hypoxia, coexistent septic vasodilitation, and the enormous oxygen cost of spontaneous respiratory effort all contribute to the hyperdynamic state so common in the early phases of acute lung injury.

## ABNORMALITIES OF OXYGEN TRANSPORT AND UTILIZATION

Oxygen delivery ($DO_2$), the total bulk flow of oxygen available for tissue utilization in milliliters per minute, is calculated as the product of cardiac output and arterial oxygen content. In normal subjects, oxygen consumption ($VO_2$) remains constant at different levels of oxygen delivery due to compensatory changes in tissue oxygen extraction ($VO_2/DO_2$). The point of maximal compensation achieved during conditions of decreasing delivery defines a critical threshold of $DO_2$ below which flow limitation of oxygen uptake occurs, and both anaerobic metabolism and lactic acidosis appear. $VO_2$ becomes "supply dependent" and exhibits a linear relationship with $DO_2$ (Fig. 2). Data in normals recovering from general anesthesia as well as in patients with congestive heart failure, pulmonary edema, and pulmonary hypertension suggest that the normal threshold of oxygen delivery below which $VO_2$ becomes supply dependent is in the range of 7 to 9 ml per kg per minute.[33,97,152] An abnormal pattern of peripheral oxygen metabolism termed "pathological supply dependency"[28] has been observed in patients with ARDS and sepsis, which is characterized by the following: (1) a linear relationship or "dependence" of $VO_2$ and $DO_2$ at levels of $DO_2$ above the normal threshold; (2) a relatively fixed oxygen extraction ratio ($VO_2/DO_2$) at varying levels of $DO_2$; (3) the tendency for $VO_2$ to increase to supranormal levels as supply in increased; and (4) a possible limitation in the maximal oxygen extraction achieved when oxygen delivery is severely reduced.[28,38B,93]

The pathophysiology and clinical significance of these changes are poorly understood. Pathologic supply dependency could occur globally if a disturbance in the autoregulatory mechanism that normally permits either tissue capillary density or organ perfusion to respond to changing oxygen availability occurred, or abnormalities of intracellular oxygen utilization were present. Factors associated with sepsis that could cause these abnormalities include interstitial edema due to increased microvascular permeability, impaired vasoregulation, or microembolization of capillary beds with cellular debris or coagulation products.[28,121] Endothelial damage in ARDS

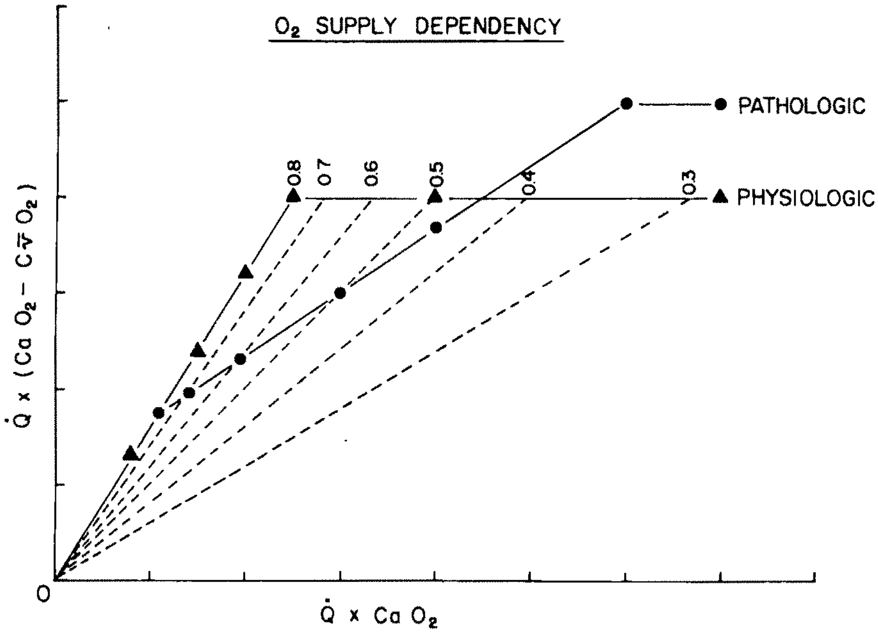

Figure 2. A schematic representation of physiologic (▲) and pathologic (●) supply dependency. Oxygen uptake ($VO_2$) is on the ordinate, and oxygen delivery ($DO_2$) is on the abscissa. Dashed lines represent isopleths of constant oxygen extraction. Numbers represent values of oxygen extraction ($VO_2/DO_2$). In this scheme of pathologic $O_2$ supply dependency, $VO_2$ and $DO_2$ are linearly related at a $DO_2$ below the normal threshold (O2Ex = .8), $VO_2$ plateaus at a high value, and oxygen extraction increases to a lesser degree as $DO_2$ is decreased. Note that the maximal extraction achieved (80 per cent) in the pathologic and physiologic curves are the same, although the former is achieved at a lower $DO_2$. (From Cain S: Assessment of tissue oxygenation. Crit Care Clin 2:542, 1986; with permission.)

could theoretically lead to systemic circulatory abnormalities by increasing the peripheral concentration of vasoactive compounds normally cleared by the lung, including serotonin, bradykinin, norepinephrine, and prostaglandins. Impaired pulmonary clearance of serotonin and $PGE_1$ has been reported in human ARDS.[67,116,142] Although the role of aberrant intracellular oxygen metabolism is uncertain, support for impaired vasoregulation comes from animal models where similar abnormalities of oxygen uptake have been reproduced after microembolization of capillary beds and alpha-adrenergic blockage. In an experimental model where pathologic supply dependency was observed after the infusion of live *Pseudomonas,* septic animals were nonetheless able to maximally increase oxygen extraction as well as achieve high levels of $VO_2$, suggesting that defects in intracellular oxygen utilization may be less important than impaired vasoregulation.[121] The limits of oxygen extraction at low $DO_2$, however, have not been well defined in clinical studies of ARDS or correlated with disease severity. We have observed a limitation of maximal extraction in patients with severe ARDS and septic shock when delivery is reduced to levels in the range of 200 to 250 ml per minute by either anemia or a low cardiac output.

Abnormal oxygen metabolism was first described in ARDS by Powers et al in a study of post-traumatic respiratory failure where oxygen consumption was found to be linearly related to delivery when the latter was altered by PEEP-mediated changes in cardiac output.[130] Subsequent studies have noted pathologic supply dependency in ARDS when oxygen delivery was altered with catecholamines, volume loading, and vasodilators.[38B,138] In many of these early studies, however, $VO_2$ was not measured independently, but calculated as the product of cardiac output and arteriovenous oxygen difference, variables also used in the determination of oxygen delivery. It has been argued, therefore, that the observed dependence of $VO_2$ on $DO_2$ is spurious, since the correlation of parameters that share a common variable is statistically unsound. A number of factors suggest that these studies are nonetheless valid, including the absence of pathologic supply dependency in control groups studied with the same methodology, the good correlation between gasometrically measured and calculated $VO_2$, and the consistency of directional changes in both variables in individual patients, but not controls.[28] Results of more recent studies, including two where $VO_2$ was measured independently, have shown that pathologic supply dependency may not be universally present in ARDS, and only quantitatively significant in subsets of patients with more severe degrees of lung injury or associated sepsis. In one study of patients with severe ARDS, for example, independently measured $CO_2$ production (and therefore $VO_2$), was not found to be linearly related to oxygen delivery above the normal critical threshold.[50] Kariman et al[90] found a greater dependence of oxygen uptake on delivery in 21 patients with ARDS as opposed to 15 controls with congestive heart failure: the correlation of $VO_2$ and $DO_2$ was increased by the presence of sepsis and related to overall survival. Wolfe et al[185] increased oxygen delivery in patients with septic shock with volume loading, noting pathologic supply dependency only in a subgroup that was hyperdynamic: patients with "low flow" sepsis had normal oxygen utilization. Bihari et al[18] modified oxygen delivery by the infusion of prostacyclin in 27 patients with septic shock and acute respiratory failure, noting pathologic supply dependency only in nonsurvivors. Differences between these and earlier studies may reflect variations in methodology, disease severity, or degree of anaerobic metabolism. Since the patterns of abnormal oxygen metabolism observed in sepsis and ARDS are similar, it is difficult to assess the effects of isolated lung injury since virtually all studies of ARDS have included heterogenous patient populations with a variable incidence of sepsis. Although pathologic supply dependency was noted to occur in a subset of patients with "nonseptic" ARDS in one study, the numbers were small, and the observation merits confirmation.

Although anaerobic metabolism and lactic acidosis have been invariably associated with physiologic supply dependency, it is unclear whether they are necessary determinants of pathologic supply dependency. Insensitivity of serum lactate as a marker for anaerobiosis could occur in shock if systemic lactate clearance or local tissue washout were perfusion dependent.[81,121] This could result in the dissociation of the threshold of oxygen delivery at which lactate production and supply dependency occurred. Alternatively, flow limitation of oxygen uptake could occur in the absence of anaerobiosis if extramitochondrial pathways were responsible for a significant fraction of oxygen uptake. The absence of serum lactate measurements in many early studies of ARDS has lead to more recent attempts to correlate lactate production with pathologic supply dependency. Annat and associates, for example, measured oxygen consumption by gas collection in eight patients with ARDS who had normal serum lactate levels and were unable to demonstrate abnormal oxygen metabolism.[7] In two recent studies of patients with septic shock, some of whom had respiratory failure, only subgroups with elevated arterial lactate concentrations demonstrated pathologic supply dependency when oxygen delivery was increased with either volume loading or blood transfusion; when delivery was increased by the infusion of catecholamines, oxygen uptake increased in the absence of lactic acidosis, implying drug-induced calorigenesis.[66,74] Mohensifar et al,[113] however, noted pathologic supply dependency in a group of patients with ARDS in the absence of metabolic acidosis.

It is unclear, therefore, whether the rise in $VO_2$ that occurs as oxygen delivery is increased to supra-normal levels in sepsis or ARDS implies the presence of an "oxygen debt," or is merely a marker for deranged metabolic autoregulation. An upper limit of $DO_2$ beyond which $VO_2$ fails to increase has not been firmly established in ARDS: in one study, scatter between $VO_2$ and $DO_2$ occurred at a $DO_2$ of 21 ml per kg per minute;[38B,113] in another, $VO_2$ continued to increase as delivery approached levels as high as 40 ml per kg per minute. Until more insight is gained into the pathophysiology of oxygen metabolism in these disorders, in particular the adequacy of lactate as a marker for anaerobiosis, and the dependence on either for the development of pathologic supply dependency, it will remain difficult to define a therapeutically optimal oxygen uptake or delivery. Although a high $VO_2$ has been associated with survival in retrospective studies of patients with multisystem organ failure,[22B] no studies to date have shown that increasing oxygen consumption in ARDS results in either a reduction of serum lactate or improved survival. Moreover, a reduction in lactate that occurs after cardiac output is increased could be the result of augmented clearance as opposed to reduced production.[9] Therapeutic strategies designed to achieve supranormal oxygen consumption by increasing cardiac output either pharmacologically or indirectly by limiting PEEP at the expense of potential reductions in $FIO_2$ are therefore tenuous.

## CLINICAL AND PATHOLOGIC CORRELATIONS

Serial changes in the relationship between lung mechanics, gas exchange, and response to PEEP have been imperfectly correlated with the pathologic and clinical couse of ARDS due to a focus on acute disease in most animal models and human studies.

In the early, or exudative phases of lung injury, alveolar flooding, collapse, and hemorrhagic interstitial edema predominate. These changes are accompanied by a marked reduction in functional residual capacity (FRC). Pressure-volume curves exhibit increased hysteresis as well as a flattening and concavity of the inspiratory limb at low lung volumes, which is followed by an inflection point above which a normalization of slope occurs. These changes are consistent with a reduction in static lung compliance at relatively low volume with the preservation of normal compliance as total lung capacity is approached.[83,109,162,172] The inflection indicates the volume above FRC where compliance normalizes, and probably indicates the lung volume where maximal alveolar recruitment or reversal of small airway closure occurs. The presence of hysteresis and early concavity on the inspiratory limb of the pressure-volume curve has been correlated with responsiveness to PEEP in patients with ARDS (Figs. 3 and 4).[109] It has been suggested that the decrease in compliance at low lung volume during acute pulmonary edema may be the result of factors related to alveolar collapse and/or airway closure rather than alterations in actual lung elastic recoil. A decrease in chest wall compliance was found in one study of paralyzed patients with ARDS,[92] however, factors such as chest wall edema or elevated intraabdominal pressure may have been involved. In an animal model of oleic acid injury, Slutsky et al reported normal chest wall compliance when thoracic volume was measured by magnetometry.[162] The role of inspiratory intercostal muscle tone as well as the effects of respiratory muscle paralysis on FRC and chest wall compliance are unknown. It is tempting to speculate that exaggerated tonic inspiratory muscle activity may be present in ARDS in an attempt to preserve FRC.

Studies of gas exchange in the early phases of lung injury with the inert gas technique have shown that the major cause of hypoxemia is shunt, with a small contribution from lung units with extremely low ventilation perfusion ratios. These studies have ruled out diffusion impairment as a cause of impaired oxygenation in early ARDS.[39,135] Although an increase in dead space is present both due to rapid shallow breathing and parenchymal edema, blood gas abnormalities are largely dominated by shunt, and typically show severe hypoxemia with a normal or low $PaCO_2$. Superimposed septic, cardiogenic, or hypovolemic shock resulting in inspiratory muscle fatigue is a common cause of $CO_2$ retention or frank respiratory arrest at presentation. In their absence, many patients tolerate the increased work of breathing and high ventilatory demand for relatively long periods of time without the development of $CO_2$ retention. The respiratory pattern is typical of interstitial disease in general, and is characterized by rapid shallow breathing and a heightened respiratory drive that results from stimulation of lung parenchymal receptors. In some patients, life-threatening hypoxia occurs, defined as a $PaO_2$ less than 50 on 100 per cent oxygen, maximal PEEP, and optimal ventilatory settings. This usually occurs during the first 12 to 24 hours after the onset of pulmonary edema and is due to extreme alveolar flooding, which may result from inadvertent fluid overload during prior volume resuscitation of shock.

If lung injury is severe and fails to resolve, a proliferative or late phase may follow over days to weeks, which is characterized by the resorption of alveolar edema, organization of hyaline membranes, mononuclear cell infiltration, and fibrosis. Coexistent vasoocclusive changes as well as fibrotic destruction of the pulmonary capillary bed may result in extensive microin-

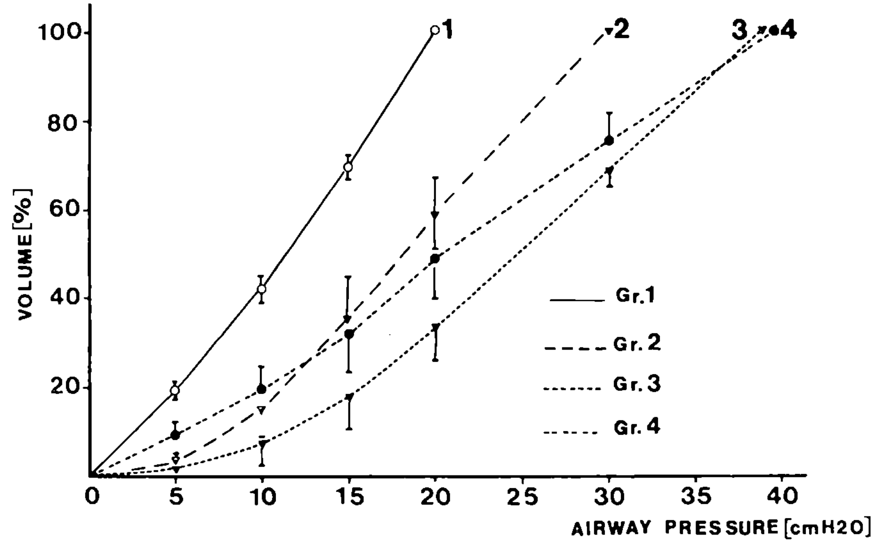

Figure 3. Mean values of 34 inflation pressure-volume curves obtained in a group of patients with ARDS. Group 1, normal compliance, no inflection. Group 2, normal compliance, presence of inflection. Group 3, decreased compliance, presence of inflection. Group 4, decreased compliance, no inflection. Groups 2 and 3 were in the early phase, group 4, the late phase, and group 1 in recovery. Note the inflection point and flattening at low volume in groups 2 and 3. In group 4, the inflection disappears and slope is reduced at all lung volumes. (*From* Matamis, et al: Total respiratory pressure volume curves in the adult respiratory distress syndrome. Chest 86:58–66, 1984; with permission.)

farction and bronchiolectasis.[167,188,192] Pressure volume curves typically show a loss of hystersis, and a reduction in slope that is consistent with a decrease in static lung compliance.[109,172] These mechanical changes have been associated with a diminished responsiveness to PEEP, and probably reflect the lack of recruitable air spaces with progressive fibrosis.[99] While mechanisms of abnormal gas exchange have been poorly studied in late ARDS, most patients experience a reduction or stabilization of shunt fraction and increases in dead space that result in the need for excessively high minute ventilations. The importance of ventilation-perfusion abnormalities as opposed to absolute shunt is suggested by the improved responsiveness to oxygen in some patients.[99] The role of diffusion impairment as a cause of hypoxia in late ARDS in the presence of marked septal thickening is unknown.

## MANAGEMENT OF ACUTE LUNG INJURY

Despite a wealth of recent insight into the pathophysiology of ARDS, the lack of specific therapy capable of reversing lung injury limits practical management to a frustratingly supportive role. Although modern ventilatory techniques have undoubtedly reduced the incidence of early death due to hypoxemic respiratory failure, they have had little impact on a persistently high overall mortality that is primarily the result of sepsis in the setting of multisystem failure.[13,128] Only 15 to 20 per cent of deaths can be attributed to respiratory failure per se, largely in the setting of end-stage disease com-

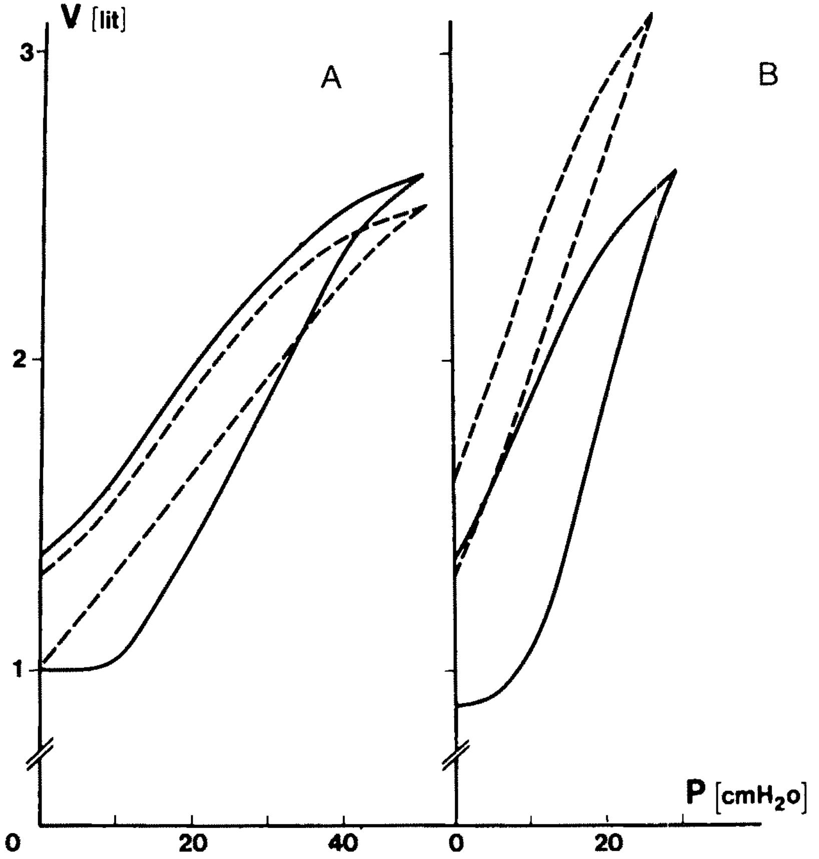

Figure 4. Successive pressure-volume curves in two patients (A and B) with ARDS during the acute phase (solid line) and either recovery (dotted line B) or fibrosis (dotted line A). Note marked hysteresis and a prominent inspiratory inflection in both patients during acute disease. In A, as fibrosis occurs, hysteresis decreases. In B, FRC and compliance improve with recovery. (*From* Matamis, et al: Total respiratory pressure volume curves in the adult respiratory distress syndrome. Chest 86:58–66, 1984; with permission.

plicated by severe fibrosis and refractory barotrauma.[115] Vigorous diagnosis and treatment of nosocomial infections is therefore a critical goal of management. Dogmatic guidelines regarding details of hemodynamic and ventilatory management are difficult to justify since few, if any, prospective studies evaluating various treatment regimens have been conducted in humans with this disease.

## INDICATIONS FOR INVASIVE HEMODYNAMIC MONITORING

Traditional clinical criteria for diagnosing ARDS include the exclusion of hydrostatic pulmonary edema with the demonstration of normal left-sided filling pressures. The generally poor correlation between wedge pressure and extravascular lung water, radiographic extent of pulmonary edema, and effective microvascular filtration pressures, limits the diagnostic accuracy of pulmonary venous pressures obtained at the bedside.[26,48] Preexistent fluid overload or underlying left ventricular dysfunction may obviously result in a high pulmonary venous pressure despite the presence of permeability pulmonary edema. Conversely, normal pressures are common in the patient with pure cardiogenic pulmonary edema if measured after therapy with diuretics and/or vasodilators. In a study of 70 patients with pulmonary edema admitted to an intensive care unit, Fein et al[51] found that right heart catheterization added little to a noninvasive clinical diagnosis of ARDS, which was accurate in most patients. Despite its obvious diagnostic limitations, right heart catheterization is useful in the management of many patients at presentation due to the frequency of occult fluid overload or cardiac dysfunction in acute respiratory failure, particularly those with multisystem organ failure, recent major surgery, and the elderly. Monitoring oxygen delivery and demonstrating hemodynamic tolerance of PEEP is often important when moderate to high levels of PEEP are required. Patients with mild disease, or those who respond rapidly to positive pressure ventilation may not require invasive monitoring. It should be noted that no studies have shown that hemodynamic monitoring improves mortality or lessens morbidity in ARDS.

## BEDSIDE HEMODYNAMIC MEASUREMENTS

Positive pressure ventilation with PEEP may artifactually elevate intraluminal filling pressures by transmission of airway pressure to the pleural space, or by direct compression of alveolar vessels to create zone I or II. The latter can be ruled out at the bedside by noting (1) preservation of cardiac waveforms on the tracing, and (2) failure of measured pressures to rise 50 per cent or more of any increment in PEEP. The former may be corrected by subtracting roughly 25 per cent of PEEP from measured intraluminal pressures. Recent data in a dog model of ARDS suggests that severe lung injury may mechanically protect the patency of vessels between the catheter tip and left atrium and therefore preserve good correlation between wedge and left atrial pressures.[73] In this model, lung injury seemed to maintain identity of wedge and left atrial pressures at levels of PEEP that would otherwise have resulted in zone I or II conditions. It is important to remember that the "wedge pressure" corresponds to hilar venous pressure when balloon inflation results in occlusion of a lobar artery and not upstream hydrostatic filtration pressure: the latter may be considerably higher in the presence of pulmonary artery hypertension and an elevated PAD-PCW gradient. Estimation of pulmonary capillary pressure may be made by using the Garr equation, or more accurately by manual inspection of the wedge tracing.[36] As discussed previously, however, pulmonary capillary pressures may seriously underestimate the effective filtration pressure in the presence of significant pulmonary hypertension. From a practical point of view, the presence of a large PAD-PCW gradient means that a pulmonary capillary wedge pressure that would otherwise be considered "low" may correspond to excessively high filtration pressures upstream at sites of edema formation, and require further reduction through the use of diuretics or other measures.

Considerable artifact frequently results when measuring vascular pressures in tachypneic patients who are mechanically ventilated. Recording of pressures at end-expiration rather than using electronic means is preferred, and may be performed by inspection of strip chart recordings at the bedside or direct inspection of monitor waveforms. At end-expiration, intraluminal pressure is closest to true transmural pressure, since pleural pressure is closest to zero (atmospheric). Identification of the end-expiratory point on the wedge tracing may be performed by finding an inspiratory dip that results from a fall in intrathoracic pressure due to the patient's spontaneous assist.

Forceful inspiratory effort that persists after the onset of the mechanical breath frequently results in a markedly negative deflection of the wedge tracing and an apparent increase in the height of the waveform at end-expiration (Fig. 5). Schuster et al[148] were the first to describe this phenomenon, showing that abolition of spontaneous respiratory effort with short-term muscle relaxation resulted in a fall in end-expiratory filling pressures that was proportional to the degree of inspiratory effort prior to paralysis. The authors argued that forceful tachypnea artifactually elevated filling pressures at end-expiration due to transmission of persistently positive airway or abdominal pressures to the pleural space in the tachypneic patient with active yet incomplete expiration at the onset of a subsequent breath. Since transmural pressures were not measured before and after muscle relaxation, however, it is equally possible that a fall in filling pressures resulted from postparalysis increases in intrathoracic pressure that could decrease preload and/or afterload, in which case changes in pressures would merely reflect alterations in the patient's physiology. Resolution of this problem, which is of considerable importance in practical bedside management, will depend on studies comparing the effect of paralysis on end-expiratory transmural filling pressures. If they remain unchanged after muscle relaxation, this would suggest that an "artifactual" elevation had indeed occurred.

## HEMODYNAMIC MANAGEMENT

Since the increased vascular permeability in ARDS effectively abolishes the normal "threshold" of pulmonary hydrostatic pressure below which fluid filtration does not occur, minute elevations in pressure may significantly increase lung water. Hemodynamic management is therefore primarily directed toward reducing the pulmonary capillary wedge pressure to the lowest level consistent with an adequate cardiac output.[133,187] In animal models of ARDS pulmonary edema responds equally when intravascular pressures are lowered by diuretics, phlebotomy, plasmapheresis, or vasodilators.[72,132] The ability of diuresis to improve oxygenation has been corroborated in clinical studies, however, the sensitivity of shunt, $PaO_2$, and lung water to the manipulation of fluid status may decrease considerably in the later phases of ARDS if vascular permeability improves. It should be noted, however, that clinical studies have generally shown a poor correlation between oxygenation and extravascular lung water in patients with ARDS.[26] This probably reflects the importance of local vasoregulation in determining the severity of ventilation-perfusion abnormalities that result from a given degree of pulmonary edema, as well as the relatively small impact of interstitial edema on gas exchange. Measurements of permeability-surface area, but not EVLW, have been shown to correlate well with both survival and oxygenation in patients with ARDS.[26] As mentioned above, fluid filtration due to elevated hydrostatic pressures along leaky vascular segments may occur with a normal pulmonary capillary wedge pressure if significant pulmonary venoconstriction or hypertension is present. Patients with life-threatening hypoxemia due to severe alveolar flooding may require a drastic reduction of intravascular filling pressures during the initial 12 to 24 hours of management to achieve an adequate decrease in

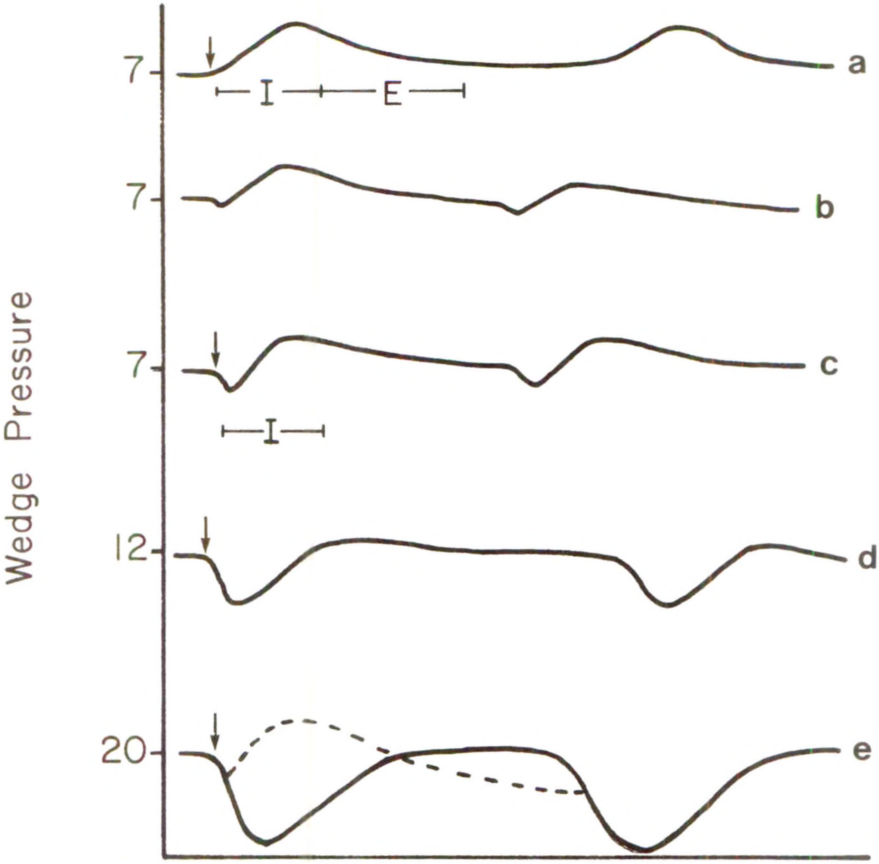

Figure 5. Schematic representation of wedge pressure tracing in the mechanically ventilated patient with increasing force of inspiratory assist. Arrows indicate end expiration. In (a), the patient is apneic, and the wedge pressure at end expiration is 7. In (b), the patient is assisting with minimal effort, which causes a small deflection in the tracing before the onset of the mechanical breath. In (e), a marked deflection of the tracing indicates forceful inspiratory effort that persists well after the mechanical breath is triggered. Wedge pressure at end expiration is now 20. Dotted line indicates the pattern of the tracing if persistent inspiration had not occurred. Paralysis at (e) would result in (a), and an apparent reduction in the wedge pressure.

shunt fraction. During this time, left ventricular preload may need to be sacrificed, and the resulting fall in cardiac output and blood pressure transiently supported with inotropic and/or pressor agents. In most patients, however, a reasonable compromise between preload and pulmonary venous pressure can be achieved.

### Use of Cathecholamines

Optimal catecholamine regimens for treatment of associated vasodilatated or low output states are undetermined. Exogenous catecholamines may promote pulmonary edema formation by raising cardiac output or pulmonary vascular pressures. In animal models, dobutamine may cause less pulmonary vasoconstriction than dopamine, however, their vasoactive effects have not been compared in ARDS.[59,84] Molloy et al[114] found that the infusion of dopamine into 11 patients with ARDS augmented cardiac output at the expense of a rise in PCW and left ventricular end-diastolic volume. Shunt fraction only increased when elevated flows were accompanied by a rise in mixed venous $PO_2$. A lack of direct arteriolar vasoconstriction was suggested by a constant PAD-PCW gradient. Jardin et al[87] studied the effects of dopamine in 15 patients with septic shock and acute respiratory failure, noting increases in both shunt and $PVO_2$ after dopamine, yet no change in arterial $PO_2$. In a study comparing the effects of dopamine and dobutamine in patients with ARDS, dopamine resulted in higher PCW pressures than dobutamine at equivalent levels of cardiac output.[43] Shunt fraction remained unchanged after both drugs. These studies suggest that dobutamine may be preferable to dopamine for isolated inotropic support in ARDS since increases in flow are not accompanied by an elevation of left ventricular filling pressure. Studies comparing dopamine and norepinephrine in ARDS in terms of their relative effects on lung edema formation, pulmonary vasoconstriction, and LV filling pressures are lacking.

### Management of Right Ventricular Failure

Although severe increases in pulmonary vascular resistance in ARDS have occasionally been associated with overt right ventricular failure, it is difficult to separate the effects of lung injury from those of coexistent septic cardiac dysfunction or underlying heart failure in clinical studies. The optimal management of afterload-induced RV failure in ARDS is unknown. The use of volume expansion to increase RV stroke volume has been shown to result in a deterioration of right ventricular function in animal models where RV failure is induced by pulmonary embolization.[134] Since RV dilitation occurs in response to increases in afterload, further infusion of volume may markedly increase wall stress and lead to profound increases in afterload or ischemia. Although right ventricular failure is virtually always associated with an abnormally elevated right ventricular end-diastolic pressure in human studies of shock due to massive pulmonary embolism, severe right ventricular dilitation frequently occurs in septic shock at low filling pressures due to a marked increase in ventricular compliance. It is likely that the dilated septic right ventrical is unusually sensitive to increases in afterload resulting from volume expansion, particularly if also confronted with an abnormally high pulmonary vascular resistance due to acute lung injury itself. The administration of catecholamines such as norepinephrine and dopamine has been reported to improve cardiac output with a reduction in both end-diastolic and end-systolic volumes in the setting of experimental RV shock.[134] Vasodilators such as nitroprusside or hydralazine have also been reported to improve cardiac output and reduce pulmonary vascular resistance in experimental ARDS, however, their use may be limited by coexistent hypotension or severe hypoxia.[64,65,158] High-frequency jet ventilation has been shown to result in a relative reduction in pulmonary vascular resistance and improved cardiac output when compared with conventional ventilation in experimental RV failure due to pulmonary emboli or surgical ablation of the right ventricle.[104,117]

### Choice of Intravenous Fluids

Although considerable controversy persists regarding the advantages of crystalloids versus colloids, attempts to increase plasma oncotic pressure with the infusion of colloid solutions has not been shown to decrease lung edema in ARDS[119]; indeed, the potential for secondary increases in hydrostatic pressure, as well as egress of administered protein into the pulmonary interstitium make use of crystalloid perferable in the early phases of lung injury. Although massive crystalloid resuscitation may result in an acute reduction in plasma oncotic pressure (COP), and hence lower the hydrostatic pressure at which alveolar flooding occurs, it is unclear that chronic hypoalbuminemia effects a reduction in the hydrostatic threshold for pulmonary edema if equilibration of interstital and intravascular oncotic pressure occurs. Brigham et al found no correlation between EVLW and the pulmonary capillary-colloid osmotic pressure gradient in a group of 14 patients with ARDS.[26] The impact of acute reductions in COP in the setting of permeability edema are of uncertain clinical significance.

Continuous monitoring of mixed venous oxygen saturation ($SVO_2$) is now possible with the incorporation of fiberoptic oximetry into commercially available pulmonary artery catheters. Changes in $SVO_2$ may rapidly reflect alterations in total oxygen delivery, tissue perfusion, and oxygen uptake in the hemodynamically unstable patient, and alert the clinician to search for underlying causes such as a fall in cardiac output or drop in hemoglobin concentration. In patients with ARDS or sepsis, however, $SVO_2$ may remain relatively fixed despite changes in oxygen delivery if pathologic supply dependency of oxygen uptake is present. These factors probably account for the poor correlation between $SVO_2$ and either lactate production or survival in patients with sepsis, and may limit the utility of $SVO_2$ monitoring in the intensive care unit.[23,136,147]

## VENTILATORY MANAGEMENT

Goals of ventilatory management include provision of adequate gas exchange, oxygen delivery, and minimization of the enormous oxygen costs of breathing. With the replacement of continuous mandatory ventilation by assisted or patient triggered modes of ventilation, practical choices for the initial management of the patient rest between a combination of PEEP with either intermittent mandatory ventilation (IMV) or assist control (AC). New ventilatory techniques such as inspiratory pressure support,[131] pressure release ventilation,[45,171] inverse ratio ventilation,[71] and extracorporeal $CO_2$ removal[61] are largely experimental and have not been adequately evaluated in prospective clinical trials or in terms of physiologic effect to recommend routine use. While a safe and effective alternative to conventional techniques, high-frequency ventilation has not been shown in a recent large randomized trial to improve either long-term survival or provide superior short-term gas exchange.[30] It may, however, have limited utility in the setting of advanced barotrauma, bronchopleural fistula, refractory hypercarbia, and in a subset of patients who fail to achieve adequate gas exchange with conventional respirators.

Despite continuing controversy and years of largely inconclusive studies attempting to compare IMV and assist control in terms of weaning, hemodynamic effect, and as modes of ventilation, no comparative studies in patients with ARDS exist. Relevant differences between the two in this setting include effects on (1) hemodynamics and tolerance of PEEP, (2) mean airway pressure, (3) V/Q matching, (4) respiratory muscle tone and atrophy, (5) respiratory alkalosis, and (6) oxygen consumption.

### Hemodynamics

The hemodynamic consequences of intrathoracic pressure are largely mediated through its effects on venous return (preload) and transmural aortic pressure (afterload). Lower pressure tends to increase preload and afterload, higher pressure the reverse, with the net effect on stroke volume highly variable and dependent on baseline volume status, ventricular compliance, and sensitivity to afterload. In general, patients with elevated baseline filling pressures who are on the plateau of the Starling curve and have systolic dysfunction tend to increase stroke volume with increases in intrathoracic pressures. Conversely, patients who are relatively volume depleted or on the ascending limb of the Starling curve with normal systolic function, tend to decrease stroke volume with an increase in pressure.[110] It is obvious that the magnitude and direction of hemodynamic changes is highly variable in a given patient. While lower intrathoracic pressure with IMV tends to increase venous return, and may decrease PEEP-mediated reduction in preload, judicious use of volume largely eliminates this "advantage" over AC.

### V/Q Matching

Positive pressure ventilation frequently results in the exacerbation of V/Q mismatch when compared with spontaneous breathing due to increased distribution of the passive, mechanical breath to nondependent and hence less well perfused lung.[56,137] The presence of interposed spontaneous breaths with IMV should theoretically lead to better gas exchange, however, no studies have compared the two in patients with acute lung injury. In a recent study of patients with normal lungs recovering from cardiothoracic surgery, breath by breath analysis of gas exchange revealed quantitatively small differences between spontaneous breaths on IMV and mechanical breaths that are of uncertain clinical significance.[186] The forceful inspiratory effort that frequently persists after the onset of mechanical inspiration in patients with ARDS may increase distribution of the mechanical breath to more dependent lung and, therefore, mitigate potential differences in gas exchange between IMV and assist control. This is suggested by an apparent increase in dead space after spontaneous assist is abolished by muscle relaxation in patients with ARDS.

### Mean Airway Pressure

Although it is tempting to conclude that the lower mean airway pressures during IMV would result in less barotrauma, little clinical evidence exists to support this notion. The incidence of barotrauma in ARDS has been poorly correlated with either mean airway pressure or level of PEEP, and may be related to other factors such as disease severity, volume status, and transpulmonary pressure.[150,188]

### Respiratory Muscle Tone and Atrophy

The notion that disuse atrophy of the respiratory muscles resulting from prolonged assisted ventilation might be prevented by exercise with IMV has not been substantiated in human studies. Moreover, the desireability of permitting spontaneous ventilation in the patient with shock or recent respiratory muscle arrest (and hence inspiratory muscle fatigue) is questionable. Recent data have suggested that considerable inspiratory work occurs in patients ventilated in the assist mode.[165]

### Oxygen Cost of Breathing

A major goal of mechanical ventilation in the patient with acute lung injury is to eliminate the enormous oxygen cost of breathing. Critically ill patients will typically increase oxygen consumption 30 to 50 per cent in the transition from mechanical to spontaneous breathing.[54] Although less data is available in human ARDS comparing the oxygen cost of different ventilatory modes, studies in a variety of clinical settings have shown that IMV results in a significant increase in $VO_2$.[89] Moreover, the increased work of breathing and reflex tachypnea in ARDS are likely to exaggerate these differences. In our experience, increased respiratory drive and reflex tachypnea result in a surprisingly high degree of inspiratory work even while the patient is ventilated in the assist mode, which may approach 20 to 30 per cent of whole body oxygen consumption.

### Respiratory Alkalosis

Avoidance of respiratory alkalosis has been long held to be an advantage of IMV over assist control, however, recent studies of critically ill patients show these differences to be insignificant in the majority of patients.[38] The loss of feedback control in ARDS due to reflex increases in central drive is manifested by the common occurrence of mild respiratory alkalosis in spontaneously breathing patients, which often persists after intubation in the assist mode. This is rarely detrimental and usually abates with renal compensation in 1 or 2 days. Severe respiratory alkalosis is relatively uncommon, and frequently results from improper respiratory settings, including inadequate inspiratory flow rates or tidal volume.

Many of the differences between IMV and assist control are of limited clinical significance and have little bearing on choice of ventilatory mode in the patient with acute lung injury. The enormous increases in oxygen consumption associated with spontaneous breathing, however, make assisted modes of ventilation preferable in ARDS. Although patients without shock, metabolic acidosis, and mild lung injury may be successfully and safely ventilated with a CPAP mask[180] or with IMV for short periods of time, most will require some form of assisted ventilation as lung injury progresses. Recent studies have focused on the high occult inspiratory and expiratory work of breathing that frequently occurs during conventional assisted ventilation. Diaphragmatic contraction often persists well beyond the onset of the mechanical breath and may be followed by premature or excessive expiratory muscle contraction. This apparently results from poor integration of mechanical flow with patient drive and timing.[145,164,165]

## VENTILATOR SETTINGS

The high respiratory drive, noncompliant lungs, and increased ventilatory demands of patients with ARDS dictates a ventilatory strategy similar to that required by patients with interstitial disease in general. Rapid inspiratory flow rates (80 to 120 L per minute) shorten inspiratory time, curtail premature expiration, and decrease "air hunger," which may increase tachypnea; they are essential for optimizing patient-ventilator synchrony. In addition, the degree of occult inspiratory and expiratory work performed by the patient during assisted ventilation is markedly reduced by an increase in inspiratory flow rates. At low inspiratory flow rates, excess inspiratory work may approach the total work done by the ventilator to passively inflate the lung.[145] The primary factor limiting flows is peak airway pressure, which rises proportionally. It is generally desirable to keep peak pressures less than 60 cm if possible, although absolute correlation of peak pressure and barotrauma is uncertain.

Choice of tidal volume can be made by selecting the volume that results in the maximal end-inspiratory static compliance, although accurate values of compliance are often difficult to obtain in the tachypneic patient who is spontaneously assisting.[83,174] As the severity of lung injury increases and lung compliance falls, smaller volumes and more rapid rates are required to avoid excessively high airway pressure in the face of minute ventilations exceeding 20 to 25 L per minute. The use of large volume "sigh" breaths has not been shown to improve gas exchange or compliance in one study of patients with acute respiratory failure,[122] and frequently causes unacceptably high airway pressure in the patient with ARDS. Inadequate tidal volumes may occasionally exacerbate air hunger and result in severe tachypnea and respiratory alkalosis.

While the use of an end-inspiratory pause has been shown to improve gas exchange in theoretical models, in one clinical study it had no effect on oxygenation, and only marginal improvement in $CO_2$ elimination, which is of uncertain clinical utility.[57] Disadvantages include a significant increase in mean airway pressure. Reports of improved oxygenation or reduced airway pressures with the use of either inverse ratio (I:E ratio of 3 to 4:1) ventilation or decelerating inspiratory flow patterns require further study before making dogmatic guidelines regarding their use.[5,129]

## PEEP

Since its introduction in 1967 by Ashbaugh and Petty, positive end-expiratory pressure (PEEP) has remained the standard technique for improving oxygenation in ARDS. Although its undoubted ability to reverse severe hypoxemia has resulted in an apparent reduction of early hypoxemic mortality, retrospective studies have failed to show an increase in long-term survival with the use of PEEP.[168] This likely reflects both an increase in late nonpulmonary morbidity, and the probable inability of PEEP to reverse the underlying pathophysiology of the disease. Although PEEP mediated reductions in $FIO_2$ undoubtedly reduce the extent and severity of oxygen-induced pulmonary damage, the quantitative impact of oxygen toxicity is difficult if not impossible to assess since its effects are pathologically indistinguishable from the disease itself.

The effect of PEEP and positive pressure ventilation on the natural history of lung injury and repair remains poorly defined. Wyszogrodski et al[189] reported that application of PEEP reversed abnormalities in surfactant function induced by mechanical hyperventilation in an animal model. Reversal of alveolar collapse and local hypoxia by PEEP could theoretically attenuate lung injury, however, such benefit is largely speculative.[184] In an animal model of ARDS, Luce et al[102] found that 24 hours of PEEP had no effect on the extent or severity of lung injury. Recently, Kolobow et al[96] demonstrated that excessively high airway pressures could induce permeability pulmonary edema in previously normal sheep subject to short-term mechanical ventilation. Kwang-Jin and Crandall[98] demonstrated increases in permeability of frog lung epithelium with hyperinflation. Studies of neonates with hyaline membrane disease have suggested improved mortality with the reduction of airway pressure during long-term muscle relaxation, and a recent report by Gattinoni et al[61] suggested that the comparative reduction in mortality of patients with severe ARDS treated with extracorporeal $CO_2$ removal and low pressure ventilation might be due to the elimination of barotrauma associated with large volume, conventional ventilation. Clarification of the effects of PEEP and positive airway pressure on the pathophysiology of lung injury remains a critical question. At present, however, there is little evidence to firmly assign a therapeutic or detrimental role to PEEP in human ARDS.

## Prophylactic PEEP

Earlier studies reporting the effectiveness of prophylactic PEEP in "high-risk" patients were largely uncontrolled and frequently marred by the lack of precise diagnostic criteria for ARDS, and hence probable inclusion of patients with simple postoperative fluid overload or congestive heart failure. In a recent prospective study, Pepe et al[124] found that the prophylactic application of 8 cm PEEP to 50 high-risk patients had no impact on the incidence of ARDS. Although it has been argued that patients who go on to develop ARDS while receiving PEEP may experience less severe initial hypoxemia or a more rapid response to positive pressure ventilation, there is no current data to support this notion.

## Hemodynamic Effects of PEEP

The hemodynamic effects of PEEP are complex, and will only be briefly reviewed here. Although PEEP may effect an increase in stroke volume in the volume loaded, afterload sensitive ventricle, it more commonly results in a depression of cardiac output, which in turn may reduce oxygen delivery in spite of a rising arterial oxygen content. Since PEEP has not been demonstrated to depress LV systolic function, its effects on cardiac output are due to either (1) decreased venous return, or (2) decreased LV compliance resulting from either RV dilitation and septal shift, or a direct increase in juxtacardiac pressure. Jardin and colleagues provided direct evidence of RV dilitation, septal shift, and impaired LV compliance in 20 patients with ARDS.[85] The authors estimated transmural filling pressures by measurement of pleural or esophageal pressure, and showed that increases in PEEP to 30 cm resulted in a progressive fall in LV and RA transmural pressure. These changes were accompanied by a decrease in the cross-sectional area of the LV due to RV dilitation and septal shift. Volume infusion that restored LV transmural pressure to baseline levels at 30 cm of PEEP failed to restore cardiac output to normal, and the authors concluded that the reduction in end diastolic volume at a given transmural pressure implied the presence of diastolic dysfunction. These conclusions may be due to the potential underestimation of true transmural pressure with the use of esophageal and pleural pressure instead of direct juxtacardiac pressure. Review of their data shows that at levels of PEEP below 30 cm, changes in cardiac output were relatively small, moreover volume infusion resulted in nearly full restoration of baseline cardiac output. No information about disease severity, baseline PAP, or PVR was supplied by the authors. Baseline LV transmural pressures for the group were 7 mm, which may have reflected relative volume depletion. In another study, Zapol et al[192] showed that PEEP as high as 30 cm had little effect on PVR or PAP in patients whose intraluminal LVEDP was 15 at baseline. In two recent studies, application of 12 to 15 cm of PEEP was not found to alter ventricular function or diastolic compliance in canine models where juxtacardiac pressure was measured directly.[53,107] In summary, clinical and animal studies have shown that moderate levels of PEEP have little clinically significant effect in the normovolemic patient on either cardiac output or diastolic LV compliance.[53,107,132,150] In the absence of excessively high levels of PEEP or severe pulmonary hypertension, decreases in cardiac output from PEEP are primarily due to diminished preload.[29,49,103,142]

## Clinical Use of PEEP

Since PEEP has not been shown to alter the natural history of ARDS, its therapeutic application is directed toward primarily improving gas exchange, oxygen delivery, and limiting oxygen exposure. As discussed above, responsiveness to PEEP is greatest in the early phases of lung injury when alveolar flooding and collapse occur, and pressure-volume curves demonstrate increased hysteresis and concavity at lung volumes in the tidal range over FRC. A number of clinical studies have shown that the level of PEEP, which raises FRC to a volume matching the "inflection" point on the inspiratory limb of the static inflation compliance curve results in a maximal improvement in shunt.[109] Additional PEEP may increase dead space by overdistending alveoli, with no further improvement in oxygenation. Correlation between optimal static lung compliance and maximal shunt reduction during the application of PEEP may be unreliable, however, in the fibrotic phase of ARDS or in some patients with excessive alveolar flooding in the acute phase. Patients with fibrosis, for example, may optimize gas exchange at a level of PEEP below that which results in the highest static lung compliance.[50B,176] Bedside measurement of the gradient between end-tidal and arterial $PCO_2$ may be a useful marker for excessive levels of PEEP, which may lead to an increase in dead space or worsen oxygenation.[118]

In most patients with ARDS, the improvement in oxygenation plateaus at levels of PEEP in the range of 15 to 20 cm $H_2O$ or *less*.[150] Although higher levels of PEEP ("super PEEP") may occasionally result in a further reduction in shunt, acceptable oxygenation is still usually possible at more moderate levels. Moreover, super PEEP is associated with a markedly increased incidence of hemodynamic side effects and possibly barotrauma. Although IMV has been advocated by some to permit the use of "super PEEP" with greater hemodynamic tolerance,[95] IMV is generally undesirable in acute ARDS; furthermore, the minimization of shunt fraction beyond levels that provide acceptable oxygenation is currently unjustified.

Since cardiac output may fall at a level of PEEP below that which results in the highest arterial oxygen content, "optimal PEEP" has been traditionally defined as that level of PEEP that results in the greatest oxygen delivery at a nontoxic $FIO_2$. Defining optimal oxygen delivery is problematic in ARDS, since abnormal peripheral oxygen utilization commonly results in linear increases in oxygen consumption at supranormal levels of delivery. Although it has been argued that increases in oxygen consumption with increasing delivery implies the presence of an "oxygen debt," neither a reversal of preexisting lactic acidosis or improvement in survival has been prospectively demonstrated in ARDS with the achievement of supranormal oxygen delivery and uptake. Limiting PEEP with the goal of increasing cardiac output and oxygen delivery to supranormal levels at the expense of potential reductions in $FIO_2$, which would be possible at higher levels of PEEP are of unproven benefit.

In an attempt to avoid the necessarily invasive monitoring required to measure oxygen delivery, a number of studies have attempted to find noninvasive respiratory parameters that correlate with oxygen delivery during the application of PEEP. Suter et al[173] studied 30 patients with ARDS and found that the level of PEEP that resulted in the highest static lung-chest wall compliance corresponded to maximal oxygen delivery as assessed by right heart catheterization. The authors did not, however, demonstrate correlation of these variables in individual patients. Subsequent studies in animal models of ARDS and in patients have shown that correlation between optimal compliance and $DO_2$ is frequently poor in both early and late phases of lung injury.[118,176] This is not surprising, since the effect of PEEP on cardiac output is highly variable, and is critically affected by factors such as volume status, severity of lung injury, and baseline cardiac function.

## ADJUNCTIVE THERAPY

### Steroids

Although steriods have been shown to be effective in inhibiting or ameliorating lung injury in animal models of septic shock and ARDS, there is little evidence to support their use in human disease.

Three major prospective trials have recently shown that a short course of high-dose methylprednisolone given early in the course of septic shock fails to improve survival, increase the incidence of shock reversal, or prevent the development of shock in patients with baseline hemodynamic stability.[141,169,181] A trend toward greater reversal of hypotension after 24 hours of therapy was noted in one study, however, simultaneous hemodynamic data were not presented.[169] The potential for even a few doses of steroids to adversely affect host flora was shown by an increase in either mortality due to superinfection or its incidence in steroid-treated groups. In a prospective, randomized study, Weigelt et al[182] demonstrated that the administration of four doses of methylprednisolone to a diverse group of intubated patients with respiratory failure nearly doubled the rate of infectious complications.

A prospective, randomized study of 99 patients with established ARDS recently showed that treatment with high-dose steroids had no impact on overall survival or short-term severity of lung dysfunction.[16] Sprung and associates prophylactically administered steroids to patients with septic shock who were at high risk for the development of acute lung injury and found no difference in the incidence of ARDS between steroid and control groups.[101,170] Evidence that steroids decrease the severity of permeability leak in human ARDS was suggested by a study demonstrating that the administration of methylprednisolone resulted in a reduction in the recovery of intravenously administered radiolabeled protein from bronchoalveolar lavage.[154] The lack of a control group, however, makes these conclusions uncertain.

### Surfactant Replacement

Endotracheal administration of surfactant has been shown to be effective in ameliorating and preventing infant hyaline membrane disease.[12,112] The finding that surfactant recovered from adults with acute lung injury is functionally abnormal has lead to interest in its potential use in patients with ARDS.[126,127] In a recent report, treatment of two patients with ARDS with endotracheal porcine surfactant resulted in a transient rise in $PaO_2$ in the absence of changes in lung compliance or FRC. The role of surfactant replacement in adults with acute lung injury remains to be determined in prospective, randomized trials.

### Hemofiltration/Ultrafiltration

The ability of techniques such as hemofiltration and plasmapheresis to lower pulmonary vascular hydrostatic pressures, increase colloid osmotic pressure (COP), and potentially clear inflammatory mediators and/or vasoactive substances implicated in the production of lung injury has lead to interest in their use in ARDS.[62] In animal models of ARDS, fluid removal with ultrafiltration or plasmapheresis to achieve an equivalent reduction in hydrostatic pressure as that produced by diuretics has been shown to be effective in reducing lung edema formation.[160] In a canine model of hydrochloric acid pulmonary edema, equal reduction of pulmonary venous pressures with hemofiltration and plasmapheresis resulted in a marked reduction in lung edema with plasmapheresis, yet little change with hemofiltration, possibly due to membrane activation of intravascular complement in the hemofilter and secondary aggravation of lung injury.[165B] Human studies have been limited to uncontrolled case reports in the setting of septic ARDS, cardiogenic pulmonary edema, and postoperative acute respiratory failure.[37,63,68,100] While effective in reducing pulmonary hydrostatic pressures, clearing radiographic pulmonary edema, and improving gas exchange, superiority over conventional therapy such as diuretics has not been shown. In two studies, improvement in pulmonary parameters after ultrafiltration was observed in the absence of a negative fluid balance, raising the question of whether clearance of vasoactive compounds and/or inflammatory mediators might have accounted for the observed clinical response.[37,68] Such benefits remain highly speculative, however. In the absence of prospective and controlled studies of a well-defined population with ARDS, the role of these techniques in the management of the nonoliguric patient remains unclear. Differences between conventional dialysis, isolated ultrafiltration or hemofiltration, and plasmapheresis in human lung injury remain to be elucidated.

### Paralysis

Although muscle relaxation is occasionally used in ARDS when life-threatening patient agitation interferes with mechanical ventilation, improvements in gas exchange are largely anecdotal, and the indications for use poorly defined. Most reports of improved oxygenation after paralysis in acute respiratory failure have been in the pediatric literature in studies of neonates with hyaline membrane disease.[76] None have reported detailed hemodynamic or gasometric data that would permit physiologic interpretation of the causes or true extent of these changes. Bishop studied the effect of paralysis with pancuronium in nine adults with acute respiratory failure, five of whom had ARDS, and found no change in cardiac output, shunt fraction, or $PO_2$ despite a significant reduction in oxygen consumption.[20] Light reported marked improvements in ventilation and oxygenation in adults with ARDS after paralysis with pancuronium; the number of patients was small, however, and data including blood gases was not supplied.[100B] Coggeshall and Marini reported improvement in oxygenation in a patient with ARDS after paralysis, which was attributed to either a reduction in shunt fraction resulting from a decrease in cardiac output or an increase in FRC.[34] In an ongoing study of the effects of short-term paralysis on gas exchange and hemodynamics in ARDS at our institution, preliminary experience suggests that paralysis frequently results in dramatic improvements in arterial $PaO_2$ in patients with pressor dependent shock and severe ARDS. Patients likely to benefit appear to have persistent and forceful inspiratory effort while in the assist mode as evidenced by a marked negative deflection of the pulmonary capillary wedge tracing during inspiration. The mechanisms underlying these improvements are unclear, yet appear to be multifactorial. In some patients, $PaO_2$ improves without changes in shunt and may be mediated by a rise in mixed venous $PO_2$ resulting from a reduction in oxygen consumption. In others, a decrease in shunt occurs, possibly due to a reduction in cardiac output, which follows the elimination of the high inspiratory work of breathing. The effect of paralysis on FRC and the pressure-volume curve of the lung and chest wall in ARDS is currently unknown. Of interest is the apparently enormous oxygen cost of respiratory assist in patients who are not overtly agitated and appear to be well synchronized with the ventilator: patients with severe disease and high respiratory drive may reduce total body $VO_2$ 20 to 30 per cent after paralysis. Although quantifying the extent of these changes and defining subsets of patients who are likely to benefit from short-term muscle paralysis remains to be done, a trial of short-term paralysis is indicated in the patient with life-threatening hypoxemia ($PaO_2$ less than 50 on an $FIO_2$ of 100 per cent and maximal PEEP) in the early phases of ARDS.

### Prostaglandin $E_1$

Prostaglandin $E_1$ ($PGE_1$) is a cyclooxygenase product of arachidonic acid that is capable of inducing vasodilitation in systemic, pulmonary, and coronary vascular beds as well as exerting profound effects on immunoregulation and coagulation. Inhibition of platelet aggregation, activation and adherence of neutrophils, and neutrophil release of superoxide anions, are among the immunomodulator effects that could theoretically make it a useful agent in septic shock or ARDS.[195] In a placebo-controlled study, the administration of high-dose intravenous $PGE_1$ to nine patients with ARDS over a 72-hour period, resulted in immediate hemodynamic effects consistent with the drug's known vasodilatory actions.[153] These included a prompt reduction in pulmonary artery pressure, pulmonary vascular resistance, and a progressive increase in cardiac index and oxygen delivery. Although calculated shunt fraction and A-a gradient were reported by the authors to have remain unchanged throughout duration of the infusion, a significant increase in $PaO_2$ occurred late in the infusion period. The significance of this change is hard to interpret, however, in the absence of detailed data regarding changes in cardiac output or mixed venous $PO_2$.

Holocroft and associates evaluated the effects of a 7-day infusion of high dose $PGE_1$ in 41 patients with ARDS in a prospective, randomized placebo-controlled study.[77] Using the $PaO_2/FIO_2$ ratio as an index of the functional severity of lung injury, the authors showed a significant increase in this ratio in $PGE_1$ recipients, but not in controls, comparing baseline values with those obtained at the time of extubation or death. Details regarding arterial blood gases, hemodynamic parameters, mode of ventilation, and fluid management were not supplied, making it somewhat difficult to assess either the significance or mechanism of these changes. More encouraging, however, was the 50 per cent reduction in 30-day mortality in the $PGE_1$ group. Overall survival was only improved, however, in a subset of patients who did not have multisystem failure. Although a lack of detailed physiologic and mortality data makes analysis of these results difficult and raises questions about potential inclusion of patients with CHF or fluid overload, the apparent benefits suggest a promising role for $PGE_1$ in the treatment of ARDS and clearly warrant further prospective trials.

## MISCELLANEOUS

Nosocomial pneumonia is a major cause of morbidity and mortality in ARDS.[149] The premorbid diagnosis of pneumonia by conventional clinical criteria including new or asymmetric infiltrates, purulent sputum, and fever has been shown to have poor sensitivity and specificity when the presence of true parenchymal infection is determined at autopsy.[6] The extreme difficulty in differentiating between colonization and infection in ARDS justifies a low threshold for antibiotic therapy. Factors implicated in the increased susceptibility of the injured lung to infection include anergy due to sepsis and malnutrition, increased epithelial binding of bacteria to oropharyngeal mucosa, depression of alveolar macrophage function, and the locally immunosuppressive effects of oxygen or other drugs.[149,151] Gastrointestinal bacterial colonization is apparently increased in the presence of alkalosis and/or ileus, and has been shown to serve as a reservoir for organisms that are subsequently aspirated into the tracheobronchial tree. This is not prevented by the presence of an inflated endotracheal tube cuff and appears to be increased by the use of nasogastric tubes. Prophylaxis of stress bleeding with agents that do not alkalinize the gastrointestinal tract such as sucralfate has been reported to decrease the incidence of gastric, pharyngeal, and tracheal bacterial colonization and may reduce the incidence of pneumonia in mechanically ventilated patients.[46]

A number of more novel and therapeutic approaches directed toward the pathophysiology of ARDS have been tried in both experimental models and some clinical trials, including antiendotoxin antibody, cyclooxygenase inhibitors, fibronectin replacement, antifibrotic therapy, oxygen free radical scavengers, and antioxidants. Their utility and role in the treatment of ARDS remains unclear.

## CONCLUSION

Despite considerable advances in supportive care, respiratory failure remains a major cause of morbidity and mortality in the patient with multisystem organ failure. Although the further refinement of ventilatory support will hopefully result from an improved understanding of the interaction between respiratory drive and pattern of mechanical ventilation, it is unlikely that survival will improve until the mediators of lung injury as well as the factors governing fibrosis and lung repair are better understood.

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# Acute Renal Failure

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Acute renal failure (ARF) is a typical component of multisystem organ failure (MOF). Rapid changes in water, electrolyte, and acid-base homeostasis, and susceptibility to catabolism compose the functional disorders of other organ systems in MOF and further complicate its management.

Approximately 5 per cent of hospitalized patients develop some deterioration of renal function.[37] Roughly 20 per cent of these patients experience deterioration, and fulminant ARF ensues.[37] ARF and MOF share several common causative factors: 50 to 60 per cent of ARF is caused by decreased renal perfusion due to hypovolemia, hypotension, or myocardial failure,[5,9,37,40-42,52] and sepsis is a contributing factor in 20 per cent of these cases.[37] The overall hospital mortality rate ranges from 40 to 70 per cent and has remained essentially constant during the last 2 decades.[5,9,14,37,40-43,52,53] When MOF is superimposed on ARF, the mortality rate is almost twice as high as it is in isolated ARF.[14,65] The unchanged high mortality rate—despite major advances in intensive care, dialysis, and filtration techniques—most likely reflects the fact that sicker patients are operated on, and advanced life-support systems now allow prolonged survival in more severely ill patients than was possible before. Consequently, ARF is more likely to occur in a sicker patient population now than it did before, often in conjunction with MOF.[14,37,53] In this context, the treatment of ARF in the intensive care unit is an integral part of the comprehensive management of MOF.

## ETIOLOGY AND PROGNOSIS

A variety of risk factors that contribute to the development of ARF are known, but only rarely can ARF be attributed to a single causative factor. For the purpose of discussion, it is useful to classify the causes of ARF as prerenal, renal, and postrenal. The pre- and postrenal causes are typically factors and events that reduce urinary excretion and that will subsequently lead to ARF if not treated promptly. Proper therapy prevents progression of

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pre- and postrenal oliguria to ARF. Once fully developed, the clinical picture of ARF and the basic principles of its management are the same regardless of the cause.

### Prerenal Causes of ARF

Hypovolemia, low cardiac output, hypotension, and vascular occlusion are the prerenal causes of ARF. Hypovolemia resulting from hemorrhage, perioperative fluid loss and fluid sequestration, and hypotension caused by septic shock are common in surgical patients. Low cardiac output without hypovolemia is usually related to severe myocardial failure, and vascular occlusion can be caused by renal artery stenosis or renal vein thrombosis. The common denominator in these causes of ARF is decreased renal perfusion. A recent study in a major teaching hospital showed that 42 per cent of ARF in their institution was caused by decreased renal perfusion and that almost half of these episodes were due to hypovolemia.[37] Cardiac dysfunction accounted for 30 per cent and septic shock for roughly 20 per cent of these episodes. In addition, ARF associated with major surgery accounted for 18 per cent of the ARF cases, and hypotension was involved in half of these. According to this study, which included more than 2200 hospital admissions, prerenal factors are involved in approximately half of all episodes of ARF.

If renal perfusion is promptly restored in the early stages of ARF caused by prerenal factors, the renal failure will be reversible, and the prognosis will be good. If hypoperfusion is prolonged, full clinical ARF will develop, and the prognosis is essentially worse. The mortality rate in ARF of predominantly prerenal cause varies from approximately 30 to 70 per cent, which is close to the mortality rate of ARF in general.[5,9,14,37,40,41,43,52,53]

### Postrenal Causes of ARF

Infrarenal, ureteral, bladder neck, and urethral obstructions are the postrenal causes of ARF. In addition, postrenal oliguria or anuria can be caused by rupture of the bladder or the urethra. The most common causes of acute obstructive uropathy are stones, tumors, prostatic hypertropy, blood clots, and traumas.[73] If the obstruction is treated without delay, or free urinary flow is secured by drainage above the level of obstruction, the prognosis for both survival and recovery of renal function is very good. In fact, the incidence of severe ARF due to obstructive uropathy is very low when compared with the incidence of obstructive uropathy. In the study of Hou and colleagues, obstruction was the cause of ARF in only 3 of 129 surgical and medical patients with ARF.[37]

### Renal Causes of ARF

Acute tubular necrosis (ATN), a variety of parenchymal renal diseases (including acute glomerulo-nephritis and interstitial nephritis), and intrarenal vascular diseases compose the renal causes of ARF.[2,32,37,73] The most common renal cause of ARF is ATN. The term acute tubular necrosis has been applied to the syndrome of ARF resulting from an acute ischemic or toxic insult to the renal parenchyma associated with prominent morphologic tubular cell damage.[2,32,73] The term may be misleading because histologic evidence of tubular damage does not necessarily correlate with functional impairment.[2,32,73] Ischemic ATN (also classified as "tubulorrhexic" according to the morphologic lesion) is associated with all types of shock, septic infections, burns, crush injuries, and transfusion reactions.[32,57] Nephrotoxic ATN can be caused by a variety of nephrotoxic substances, such as antibiotics (especially aminoglycosides), radiographic contrast agents, organic solvents, and heavy metals. The incidence of ATN is difficult to define because the diagnosis is mainly clinical and the common classifications of "ARF of prerenal origin" and "ischemic ATN" by necessity overlap. Hou and coworkers[37] found that ARF associated with administration of aminoglycosides or contrast media accounted for 19 per cent of all cases of hospital-acquired renal insufficiency. This percentage is likely to be an overestimation because of the criteria used in the study. Nevertheless, this group also observed that decreased renal perfusion, postoperative renal insufficiency, and the administration of aminoglycosides or radiographic contrast agents accounted for almost 80 per cent of all episodes of hospital-acquired ARF in surgical and medical patients.[37] This suggests that ATN and prerenal ARF are by far the most common causes of ARF in patients under intensive care, in general, and especially in patients with MOF.

### Oliguric Versus Nonoliguric ARF

The classic clinical course of ARF is an acute decrease in urinary output and increasing azotemia, followed by a diuretic or polyuric phase and slow recovery of renal function.[32,73] However, acute renal insufficiency is more commonly nonoliguric than oliguric. Recent studies suggest that only one fifth of the patients with ARF become oliguric.[37,55] The prognosis in nonoliguric ARF is also significantly better than in oliguric ARF: Mortality in oliguric ARF may be three times higher than in nonoliguric ARF.[37,55]

## PATHOPHYSIOLOGY

The pathophysiology of the development of ARF is controversial despite extensive research. Much of the controversy is probably due to use of widely varying experimental models, which do not necessarily reflect the pathophysiologic events in human ARF. Nevertheless, the main theories will be reviewed briefly.

### Renal Hemodynamics in ARF

Some investigators have proposed that increased renal vascular resistance and reduced cortical blood flow are important in the development of ARF.[3,17,29,35] In contrast to this theory, others have demonstrated severe renal failure in several different experimental ARF models despite well-maintained, or even elevated, renal blood flow.[8,18,25,64,68,71] Redistribution of renal blood flow from the cortex to the inner cortex has been observed both in experimental ARF and in humans.[64,71] Conversely, the redistribution can occur considerably later than the initial changes in renal function.[71] Multiple indicator dilution techniques have demonstrated a pattern of suppressed glomerular filtration despite relatively well-preserved renal blood flow in human ARF.[64] These studies have also provided indirect evidence for a very low glomerular filtration pressure caused by afferent vasoconstriction and postglomerular, efferent vasodilation. Several vasoactive drugs, for example, phentolamine and prostaglandin E1, increase renal blood flow but do not increase the filtration rate, presumably because of simultaneous efferent vasodilation.[63,64]

Another hypothesis, based on experimental studies, suggests that tubular damage is the primary pathophysiologic event, which, in turn, triggers the activation of the renin-angiotensin system, stimulating local formation of angiotensin II and producing constriction of the glomerular arterioles.[49] According to this hypothesis, this tubuloglomerular feedback prevents the glomerulus from supplying normal amounts of filtrate to an epithelium that is unable to reabsorb it. However, locally released angiotensin would account for afferent vasoconstriction but not for postglomerular vasodilation.[64] Tubulocellular damage may cause the release of other vasoactive substances, such as histamine, bradykinin, serotonin, or cellular metabolites, which may well account for the renal hemodynamic pattern of ARF.[64]

### Obstruction of the Tubular System

The hypothesis of tubular obstruction as the primary cause of decreased renal function is based on microscopic observations of interstitial edema, tubular casts, and regenerating tubular cells.[10,32,73] The significance of these observations has been challenged by data suggesting that many of the observed obstructive changes actually occur postmortem.[10] Furthermore, tubular casts are not consistently present, and pressure measurements within the tubular system give conflicting results.[32,49,55,64,73] Although increased tubular hydrostatic pressure resulting from casts may reduce glomerular filtration by reducing the pressure gradient across the glomerular capillary wall, this situation is not consistently present in ARF.[49,71]

### Tubular Leakage

According to the "passive backflow hypothesis," glomerular filtrate diffuses back from the damaged tubule to the interstitium.[49,55,64,71,73] The volume and the weight of the kidney do increase in ARF, and microscopic examination shows interstitial edema.[10,64] The contribution of these changes to reduced glomerular filtration is not clear. A mechanical compression of the renal vasculature is not in accordance with the observation of preferential reduction of glomerular filtration while renal circulation is relatively well preserved.[64] A combination of backflow and afferent arteriolar vasoconstriction caused by a tubuloglomerular feedback may be the cause of the reduced filtration.[55]

There is considerable data supporting each of the mechanisms described here. Nevertheless, it is likely that the primary insult on renal function initiates a sequential chain of events that are interrelated, may not all occur, and in which one of them may predominate.

## DIAGNOSIS

The diagnosis of oliguric ARF is based on the reduction of urinary output below the arbitrarily defined rate of 400 ml per 24 hours. Using 0.5 ml per kg per hour as the rate below which a patient should be considered oliguric would be a more useful criterion in the intensive care setting. Prerenal factors should be evaluated first by careful physical examination: assessment of circulating blood and functional extracellular volume, and the adequacy of cardiac output. If there is doubt, invasive monitoring techniques are indicated to assess the volume status and the cardiovascular performance, especially in MOF. The use of Swan-Ganz catheterization is recommended for this purpose in MOF. If there are no clinical signs of hypervolemia, a volume-loading test can be used as a diagnostic and often therapeutic trial. This can be done, for example, by the rapid infusion of 1000 ml of Ringer's lactate in 30 minutes, accompanied by careful evaluation of hemodynamics and urinary excretion. Significantly increased urinary output within an hour suggests prerenal oliguria. Postrenal causes of oliguria should also be evaluated. The bladder should be catheterized, and if bilateral ureteral obstruction is suspected, ultrasound, computed axial tomography, or retrograde ureteral catheterization should be performed. Unilateral ureteral obstruction is unlikely to cause oliguria if the contralateral kidney and ureter are normal. The injured oliguric patient should also be evaluated for urethral or bladder rupture.

The diagnosis of nonoliguric ARF is based on laboratory tests; increased serum urea and creatinine in the absence of oliguria indicates the development of nonoliguric ARF. Changes in creatinine clearance precede the changes in serum creatinine and can be used as an early marker.[55]

Laboratory tests are useful not only in monitoring the progression of ARF but also, with some limitations, in the differential diagnosis of ARF.[2,32,73] Tests commonly used for this purpose include determinations of urinary sodium concentration, serum and urine osmolality, the ratio of urinary creatinine to plasma creatinine concentration, free water clearance, and the fractional excretion of sodium.[2,26,32,55,73]

Urinary sodium levels less than 20 mM per L suggest prerenal oliguria, but they are not specific.[2,26] Urine osmolality tends to increase in prerenal oliguria, that is, the urine becomes more concentrated. A difference between urine and serum osmolality of more than 100 mOsm per kg suggests prerenal oliguria.[2] Free water clearance is calculated[39] as

diuresis (milliliters per minute) − osmolar clearance (milliliters per minute),

where osmolar clearance is

(urine osmolality/plasma osmolality) × diuresis (milliliters per minute)

Free water clearance expresses the amount of solute free water that is excreted or conserved per minute. Increasing free water clearance from the normally negative values toward neutral or positive values may indicate the development of ARF.[11] The fractional excretion of sodium, defined as

(urinary sodium/plasma sodium) × (plasma creatinine/urinary creatinine) × 100 per cent,

has been used in the differential diagnosis of ARF. Oliguric ATN, nonoliguric ATN, and urinary tract obstruction are associated with a fractional excretion of sodium greater than 1 per cent, whereas prerenal oliguria and acute glomerulonephritis are generally associated with values less than 1 per cent.[26] However, hemodynamic monitoring and advanced imaging techniques in the modern intensive care setting can largely replace these tests in the differential diagnosis of ARF.

All these tests are rather nonspecific and should be applied with caution because considerable overlapping among the diagnostic groups exists. Furthermore, the use of diuretics and osmolar diuresis secondary to mannitol administration or glucosuria will distort the results unpredictably; hence, the tests should not be applied in these circumstances.

## THERAPEUTIC CONSIDERATIONS

The general therapeutic principles of ARF are well established: (1) careful hemodynamic monitoring and vigorous treatment of observed disorders, especially hypovolemia and myocardial failure, in order to avoid further deterioration of renal function; (2) early dialysis to prevent serious metabolic complications, such as hyperkalemia, severe acidosis, fluid overload, and accumulation of toxic metabolites; (3) metabolic monitoring and nutritional support to avoid or minimize the deterioration of nutritional status caused by the hypercatabolism common in ARF.[5,9,27,28,40,41,43,44,52,53] Recently, new filtration techniques have been applied in ARF, and they may prove beneficial for the overall management of these patients.[2,7,24,34,50,60] Because no specific treatment for ARF exists, the principal goal of all treatment is to maintain the patient in an optimal condition so that the kidneys can recover.

### Potential Therapies for the Protection of Renal Function

Because nonoliguric ARF has a significantly better prognosis than oliguric ARF, therapeutic efforts have traditionally focused on maintaining urine flow during ARF and preventing the development of ARF by administering diuretic drugs, such as mannitol and furosemide, and, more recently, dopamine, which is known to increase renal blood flow, glomerular filtration, and sodium excretion.[2,14,32,51,73] Despite the well-confirmed effects of these drugs on certain aspects of renal function in both experimental and clinical ARF, no controlled studies exist to confirm the efficiency of these therapeutic measures in preventing ARF or altering its prognosis in human beings.

***Mannitol.*** Clinical studies in the late 1950s and early 1960s suggested that mannitol, an osmotic diuretic, was able to prevent ARF after aortic aneurysmectomy and in jaundiced patients undergoing surgery.[6,14,30] The mechanism of ARF was believed to be glomerular filtration failure resulting from tubule obstruction with cell debris and heme pigments. Maintaining tubular flow was believed to prevent the obstruction and maintain glomerular filtration.[14,56,73] This mechanism of ARF has since been questioned, and various experimental studies of the effects of mannitol on renal function in ARF have given conflicting results.[13,31,56,75] The preventive or therapeutic effects of mannitol in clinical ARF have not been demonstrated in controlled clinical studies either.[56] The results of the early clinical studies may even have been secondary to increased blood volume rather than to any direct effect on glomerular filtrations.[14] Nevertheless, mannitol does increase renal blood flow and glomerular filtration in some models of experimental ARF.[13,20,31] Expansion of the extracellular space with isotonic or hypertonic mannitol resulted in the maintenance of glomerular filtration in norepinephrine-induced ARF in dogs, whereas similar extracellular volume expansion with saline had no such effect.[20] Conversely, volume expansion with saline alone and administration of hypertonic mannitol had similar effects in myoglobinuric ARF in the rat.[75]

It is possible that these conflicting results reflect differences in the pathophysiology of ARF in the various experimental models.

***Furosemide.*** The loop diuretic, furosemide, is commonly used in large doses to increase urinary excretion in ARF.[2,12,14,32,73] It has been claimed that furosemide markedly increases urinary output, shortens or prevents the oliguric phase of ARF, decreases the need for dialysis, and hastens the recovery of renal function.[2,15,16,32,73] It produces natriutesis and dilatation of renal vasculature and increases blood flow in the normal kidney.[36,47] Its effects on renal function in ARF remain controversial. Some experimental studies have shown no advantage from furosemide administration,[33,46] whereas several experimental studies have suggested that furosemide may prevent oliguric ARF.[23,45,58,74] When furosemide is given before temporary interuption of renal perfusion in the rat, the duration of postischemic oliguria and the decrease in glomerular filtration are reduced.[45] A controlled clinical study in patients with established ARF demonstrated that large doses (3 gm per day) of furosemide were able to reverse or prevent oliguria but had no effect on the number of dialysis treatments needed, the duration of ARF, or the prognosis.[12] Another controlled study showed no effect on the duration of oliguria, the number of dialysis treatments needed, or the duration of ARF.[42]

***Dopamine.*** The cathecolamine, dopamine, when administered in low doses (1 to 4 μg per kg per minute), produces renal and mesenteric vasodilation in human beings, with little or no systemic hemodynamic effects.[51] Dopamine increases urinary output and renal function in oliguric patients after cardiopulmonary bypass,[21] in congestive heart failure,[51] in septic shock,[22] and in postoperative and intensive care patients with oliguric ARF.[59] In general, urinary output, natriuresis, and indexes of renal plasma flow and glomerular filtration increase. Experimental studies indicate that the renal vasodilating action of dopamine persists even when pressor doses of norepinephrine are given.[66] No controlled data on the effects of dopamine on the duration of ARF, the requirement for dialysis, or the prognosis of ARF are available. It is not known if dopamine remains beneficial for renal function if given for prolonged periods.

### Dialysis and Hemofiltration

Prevention of the serious metabolic complications of ARF is based on early dialysis.[5,9,27,28,40,41,43,44,52,53] One recent study on survival in postoperative ARF suggested that the interval from the onset of ARF to the first dialysis treatment and the maximum serum creatinine level prior to the first dialysis treatment are the only factors contributing to the prognosis, which might be altered by therapy.[19] The choice between hemodialysis and peritoneal dialysis depends on the clinical condition of the patient, but hemodialysis is generally the more practical choice in patients with MOF. Recently, arteriovenous hemofiltraion has gained in popularity for renal replacement therapy in patients with ARF and MOF.[7,24,34,50,60] Fluid overload, hyperkalemia, and severe metabolic acidosis can be rapidly corrected by hemodialysis. Conversely, hypotension and hypoxemia are common complications of hemodialysis and can be particularly harmful for the patient with MOF. These patients may also be more susceptible to the development of hypotension during hemodialysis,[48,61] though the risk may be reduced by using bicarbonate buffer instead of acetate.[38,62] The advantage of hemofiltration is the slow, continuous removal of water and solute, and, hence, a more stable internal body environment. This is likely to improve patient tolerance and facilitate the management of fluid balance and nutrition.[7,24,34,50,60]

### Mechanical Ventilation and Renal Function

Mechanical ventilation is associated with a tendency toward sodium and water retention.[54,67] Glomerular filtration, renal blood flow, and urine excretion may be markedly reduced during controlled mechanical ventilation.[69,70] Factors that probably contribute to this include reduced venous return and cardiac output and neural and hormonal reflex mechanisms.[54,67,69,70] The negative effects of increased airway pressure on renal function have been at least partially reversed in both clinical and experimental studies by the application of intermittent mandatory ventilation instead of controlled mechanical ventilation.[69,70] The effects of mechanical ventilation on renal function in patients with ARF and MOF have not been confirmed.

### Nutrition in Acute Renal Failure

Nutrition is an essential part of the supportive therapy for ARF.[27,28,44] Because ARF usually develops as a consequence of severe illness or injury, the metabolic effects of the primary disease. The majority of patients are hypercatabolic; therefore, nutritional depletion may develop rapidly.[72,144] A potential specific role of nutrition, and especially of total parenteral nutrition, was suggested by studies reporting enhanced metabolic stability, recovery of renal function, and improved survival in ARF from the use of total parenteral nutrition.[1,44] Several other studies have demonstrated no effect of parenteral nutrition on survival.[27,28,72] Nutrition should be regarded as an integral part of the management of ARF, but its role is obviously supportive.[72]

## PRACTICAL THERAPEUTIC GUIDELINES

Once oliguria or the biochemical markers of declining renal function (uremia, increased creatinine, decreased creatinine clearance) are observed, the patient should be examined for the cause. The prerenal causes (hypovolemia, low cardiac output, hypotension, and vascular occlusion) and the postrenal causes (obstructive uropathy or bladder or urethral rupture) should be evaluated and promptly treated if present. Treatment of these conditions without delay represents the only uncontroversial, effective preventive measure for ARF. In the normovolemic patient, attempts to maintain urinary output with drugs may convert the ARF to a nonoliguric form. Although nonoliguric ARF in general has a better prognosis than oliguric ARF, the effects of the diuretic drugs (dopamine, mannitol, furosemide) on the prognosis of ARF have not been documented. The use of dopamine for improvement of renal function is probably the least controversial; dopamine infusion at the low rate of 1 to 4 μg per kg per minute results in improved renal blood flow and function in various clinical conditions. Its physiologic mode of action and lack of side effects make it an attractive first choice in the treatment of ARF in MOF. If normovolemia has been established and the urinary output has not improved, a trial with mannitol is justified; 10 to 15 gm of mannitol infused in 15 minutes may improve urinary output. This dose can be repeated within 30 to 60 minutes. If no substantial increase in diuresis occurs, the administration of mannitol should be discontinued. If a good response is obtained, further mannitol administration may be considered if careful monitoring is provided. Overdosage can cause hyperosmolality and hypervolemia. Increasing doses of furosemide may also result in improved diuresis. If a good response is obtained, further administration seems advisable. However, in established oliguria, even very large doses of furosemide (up to 3 gm per day) have no effect on the prognosis or recovery of renal function, despite the fact that useful amounts of urine output may be induced. High doses of furosemide are ototoxic and may potentiate the nephrotoxicity of cephalosporins and aminoglycosides.

Indications for dialysis or hemofiltraiton in ARF include hypervolemia, progressive acidosis, hyperkalemia, and rapidly increasing azotemia. Fluid removal is often indicated to facilitate sufficient nutrition. Hemofiltration is an attractive alternative for the patient with MOF because of its lack of hemodynamic and respiratory side effects. Relatively high flow rates are needed, though, for adequate control of urea accumulation.

Proper nutrition should be established early in ARF. Use of enteral nutrition is rarely feasible in the patient with MOF and, hence, total parenteral nutrition is needed. The volume of fluid is not a limiting factor if dialysis or hemofiltration is applied. The nutrition program of an average adult should contain approximately 35 to 40 kcal per kg of energy daily, given as both fat and glucose, and 1 gm per kg of amino acids, given in both essential and nonessential amino acids. The exact nutrient requirements in ARF are not known.

## SUMMARY

ARF frequently accompanies MOF, and its mortality rate in conjunction with MOF is almost twice as high as in isolated ARF. Maintenance of adequate renal perfusion, critical use of nephrotoxic agents, and aggressive treatment of sepsis are the best preventive measures. Once ARF has developed, early dialysis, hemodynamic monitoring and prompt therapy for observed disorders, and metabolic monitoring and therapy are the established therapeutic principles.

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# Hepatic and Splanchnic Response in Multiorgan Failure

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The incidence of multiorgan failure (MOF), first defined by Baue et al,[1] has increased since early resuscitation treatment has improved. The incidence of MOF in critically ill patients is 5 to 10 per cent,[32] with a mortality rate of 60 to 80 per cent depending on the number of organs involved and the control of infection.[32,25] Failure occurs simultaneously or sequentially in different organs, suggesting a common etiology. Although the sequence of organs involved is variable and unpredictable, the lungs are often the first to be damaged, or at least to manifest functional disturbances before renal, hepatic, hematologic, and gastrointestinal (GI) impairment.[25] However, the damaging process also involves the GI tract and the liver very early, resulting in important morphologic and functional changes. But because of the paucity of specific GI symptoms, the GI dysfunction is not recognized immediately unless particular attention is given to the problem.

Recently the probable role of the GI tract in the ongoing pathogenesis of MOF has been discussed.[13] Organ ischemia and sepsis are the main factors implicated in the development of MOF. But the link between these factors and the multisystemic damage is still unclear. Moreover, despite extensive investigation, sometimes no causative bacterial agent can be identified. This raises a question about the role of sepsis as an etiologic factor in MOF development. Its role as a catalyzer, however, can not be denied, as will be discussed later.

The mechanism of injury is thus probably due to a generalized ongoing inflammatory reaction with activation of the complement, as seen in trauma, pancreatitis, hemorrhagic shock, and sepsis. The prolonged activation of the complement results in production of split products, inducing exaggerated aggregation of polymorphonuclear white blood cells (PMN) and thrombocytes in the microcirculation. These aggregates liberate their toxic contents (thromboxane A2, leukotriene), inducing endothelial damage. Edema develops secondary to the increase in microvascular permeability.

Oxygen free radicals, generated in a greater amount by the activated granulocytes, also seem to play a role in the ischemic gastric, intestinal, hepatic, and pancreatic reperfusion damage. The oxygen free radicals pro-

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duced exceed the enzyme superoxide dismutase-type capacity and accumulate locally where they exert their cytotoxic effect.[72] The following discussion will focus on the dysfunction of the different parts of the GI tract and will attempt to show the extent to which they participate in the progression of multisystemic organ failure.

## STOMACH

### Incidence and Clinical Setting

Up to 100 per cent of critically ill patients show evidence of stress lesions in the upper GI tract.[60] In the stomach, stress lesions range from purpuric maculae and superficial erosions to erosions involving mucosal and submucosal tissue, and blood vessels. The lesions are usually multiple, suggesting a generalized diffuse disease. Massive GI bleeding or perforation, although rarely encountered today because of the use of prophylactic treatment (5 to 7 per cent), are still associated with a mortality rate as high as 80 per cent.[94]

Lesions have been classified as acute stress ulcer, Cushing ulcer after head injury, and Curling ulcer in burns. Today this classification is not so evident and head trauma patients are described with early mucosal injury similar to that encountered in other groups of critically ill patients. It seems that the so-called Cushing ulcer looks much the same as stress gastritis in the acute stage and might not be a separate entity, or it might represent a late development to the typical more profound lesion described as Cushing ulcer.[56] Lesions appear most commonly in the fundus and spread distally as the local injury progresses. The antrum in the duodenum may be involved too, but this always occurs in conjunction with more proximal lesions of the stomach.[60]

Widespread use of endoscopy has shown that erosive gastritis develops soon after injury. Endoscopy performed in head-trauma patients showed lesions 24 to 48 hours after the injury in most of the patients.[56] As the patients recover from the acute insult and the mucosal gastric defense mechanisms are restored, the lesions heal within 10 to 14 days.

### Risk Factors

Sepsis, hypotension, respiratory failure, jaundice, and renal failure have been recognized as risk factors for bleeding from stress ulcers.[92] The low intragastric pH has been proposed as an important exogenous factor of stress ulcer and bleeding. Prophylactic measures thus attempt to keep intraluminal pH at values higher than 4. The inability to maintain pH at this value with the help of antacids or H2-receptor antagonists has been related to the seriousness of the illness, but more specifically is considered as a sign of severe sepsis.[62] This occurs usually within 48 hours from the onset of sepsis. On the other hand, drainage of a septic focus with clinical improvement is associated with favorable response to antacid treatment with a rise of intraluminal pH greater than 4. Sepsis appears as a significant determinant in the development of bleeding, especially when the septic focus is pulmonary or intraperitoneal.[61]

### Pathogenesis

Several factors are involved in the development of acute stress lesions, such as blood flow, acid-base status, mucosal permeability, mucosal secretory state, the presence of protective agents in the mucosa, and the action of damaging agents. Their relative importance is still undetermined.

***Mucosal blood flow.*** Ischemia is commonly related to gastric ulcerations and probably results from the sympathetic splanchnic vasoconstriction in response to shock. In head trauma and burn patients who later develop stress lesions, the gastric mucosal blood volume was only 36 per cent of that of a healthy control group, whereas no difference was observed in those patients who did not develop stress lesions.[50]

A fall in mucosal blood flow decreases the oxygen delivery and impedes the aerobic metabolism reducing the gastric mucosal adenosine triphosphate (ATP) content,[64] with failure of the Na/K pump resulting in swelling and death of the surface cells. This may explain why the corpus and the fundus, whose metabolism is mainly aerobic, are more prone to stress lesions than the antrum. Others have claimed that the antrum is probably less permeable to $H+$ ions.[54] However, a severe reduction (as much as 60 per cent) in mucosal blood flow is necessary to reach a significant fall in cellular $PO_2$.[7] Furthermore, in sepsis, normal or mildly reduced gastric flow coexists with signs of epithelial hypoxia.[80] Open arteriovenous shunts in the submucosa have been observed in the stomachs of burned patients and they could be due to the release of vasoactive hormones.[77]

***Acid-base status.*** Acid ions ($H^+$) in the lumen of the stomach are commonly considered essential for the development of stress lesions. But in the early shock period in which lesions are thought to develop, acid secretion is decreased. Indeed, when blood flow decreases to values less than 38 ml per min per 100 gm, acid secretion and oxygen consumption diminishes.[74] It is only later that the acidity in gastric aspirate of the critically ill increases to higher values. Even if excess $H^+$ in the lumen of the stomach is not the direct cause of stress lesions, it might, however, aggravate them.

Recently, interest has focused on the importance of the intramural pH of the mucosa. A close correlation exists between acute gastric ulceration and intramural acidification in animals.[53] The intramural pH is dependent on the local cell production of $H^+$, but is also influenced by the intraluminal pH as part of the intraluminal $H^+$ also contribute to "back diffusion" into the mucosa. In normally perfused mucosa, the $H^+$ do not accumulate because the blood flow clears the mucosa from the excess acid ions. In rabbits, increased luminal $H^+$ up to a concentration of 80 mmol per L causes a compensatory increase in blood flow, preventing the mucosal accumulation of $H^+$; any further increase overcomes the circulatory compensatory mechanism and ulceration occurs.[95] During ischemia, $H^+$ ions are produced in excess in the mucosa because of tissue hypoxia and deficient energy metabolism; in addition, $H^+$ accumulate by back diffusion. But the ability of the circulatory system to carry away the $H^+$ ions is diminished and the pH of the mucosa rapidly falls to levels that may become noxious. This suggests that ulcerations in shock are probably less due to anoxia than to impairment of local buffering capacity. The theory of "interstitial acidification" could explain why bleeding still develops in some patients despite proper neutralization of intraluminal acidity. Fiddian-Green monitored the intramural pH of 103 critically ill patients and observed that stress lesions occurred only in patients whose intramural pH fell below the lower limit of normality.[7,24,30]

***Secreting state of the mucosa.*** The secreting state of the gastric mucosa has only recently been recognized as an important protective mechanism. $HCO_3^-$ indeed is probably an important factor in the control of intramural pH. In the actively secreting mucosa, $HCO_3^-$ is produced in an amount equal to that of acid secreted by the oxyntic cells. This phenomenon is called the alkaline tide. The bicarbonate from the alkaline tide and from the blood flow neutralize the acid $H^+$ originating from back diffusion and keep intramural pH within normal limits. Studies in animals have shown that histamine-stimulated gastric mucosa offers better protection against intraluminal pH.[70] This might explain the failure of some H2-receptor antagonists to prevent ulceration because they suppress the alkaline tide and thus the intramural pH is more susceptible to decreases.

***Protective agents.*** Mucus is secreted by the gastric surface epithelial cells above an unstirred water layer at the luminal surface. Biocarbonate is secreted into this layer and the capability of mucus to maintain a high concentration of $HCO_3^-$ at this site will allow neutralization of $H^+$ diffusing from the lumen. This ability of the mucus seems to depend on gel proprieties and gel thickness.[14]

Prostaglandins (PGEs) have antisecretagogue and cytoprotective agents. Their cytoprotective effect is probably independent of their antisecretagogue action as PGE has been showed to protect gastric mucosa at much lower doses (1 per cent) than the doses needed to inhibit $H^+$ secretion. The PGEs increase mucus gel thickness and gastric bicarbonate secretion. In addition, they enhance mucosal blood flow.[66]

Carbonic anhydrase enzyme present in large concentrations in the gastric mucosa seems to stimulate a proton-extruding pump by which the stomach resists the influx of acid.[54]

***Aggressive agents*** Bile salts and other constituents of duodenal juice such as lysolecithin contribute to acute lesion formation by enhancing mucosal permeability. Gastroduodenal reflux is common in critically ill patients. Prevention of duodenal reflux reduced significant gastric lesions in dogs submitted to hemorrhagic shock.[42] Bile salts produce a decrease in active transport of $H^+$, decreasing the ability of the mucosa to tolerate the luminal pH. Pepsin, considered with intraluminal acid as a prerequisite for ulcer formation, apparently only plays a role by promoting the digestion of the necrotic tissues.

Oxygen-derived free radicals have been advocated recently as playing a major role in the pathogenesis of ulceration produced by hypotensive ischemia in rats. How the free oxygen-derived radicals produce the damage observed during reperfusion is still unclear. Their action seems to result in lipid peroxidation and cellular membrane damage, with release of intracellular enzymes leading to further injury. In addition, they seem to degrade the hyaluronic acid, a principal component of the epithelial basement membrane, causing mucosal damage. Ischemia-induced lesions after hemorrhagic shock were significantly reduced by the previous administration of the oxygen scavenger, superoxide dismutase (SOD) or of allopurinol, a specific inhibitor of xanthine oxidase.[49]

### Clinical Implications

In view of the persistent high mortality associated with acute gastrointestinal bleeding, it is clear that prophylaxis for stress ulceration is much more effective than therapy. Further improvement in early resuscitative measures should be the first concern. The accumulation of $H^+$ ions in either the serum, the interstitium, or the lumen is noxious to the gastric mucosa. However, interstitial acidification seems to be the most important step in ulcer formation. Intramural pH can easily be monitored by using the equation of Henderson and Hasselbalch with the $PCO_2$ of the gastric fluid and the arterial blood $HCO_3^-$ and can serve as a guide to predict those patients at risk and to modify therapy to prevent extreme decrease of pH values in the interstitium. This is best achieved by maintaining adequate oxygen delivery and blood flow to drain $H^+$ ions from the cells, by maintaining the mucosa actively secreting so as to enhance the capability of the cells to neutralize acidity, and by neutralizing luminal pH to decrease back diffusion.

As the incidence of acute ulcerations increases proportionally with the superimposed risk factors, any attempt to remove these predisposing factors should be made. Among them, sepsis is the main reason for inability to control gastric pH and for persistent stress lesions, and it should be aggressively treated.

Enteral feeding has long been recognized effective in preventing stress ulceration[59] and should replace the antacid therapy as early as possible. It has the advantage of improving the nutritional status of the patients and has no side effects of bacterial proliferation due to alkaline pH produced by antacids.[46] However, intolerance to enteral feeding is often encountered in the most critically ill patients and parenteral nutrition then should be adequately provided. In rats, starvation alone raises the incidence of ulcer in the nonglandular stomach, and the association of starvation and stress increases the incidence and the severity of lesions in the glandular stomach. The gastric mucosal damage can significantly be suppressed by parenteral nutrition.[68] The use of cytoprotective agents is still under investigation and might offer prospective amelioration in treatment.

## SMALL BOWEL

### Incidence and Clinical Setting

Lesions appear as confluent or isolated red areas of necrosis in the mucosa without evidence of vascular occlusion and without relation to the vascular pattern. They are often associated with stress ulceration in the upper GI tract. At microscopic examination, muscular layers of the bowel are usually intact, but the mucosa with its high metabolism is more sensitive to ischemia. Mucosal thickness will be decreased with decreased villous height and villous epithelial necrosis. The undifferentiated stem cells from the intestinal crypts are less sensitive to ischemia and might be spared. This may explain the ability of the small intestine to regenerate rapidly.

In human beings, there are so few specific symptoms when the small bowel is injured that adequate evaluation of the severity of the injury is very difficult to perform. In a series of 370 postmortem examinations performed in acute cardiovascular patients, hemorrhage and ulceration of GI mucosa were present in 33 per cent of the patients, whereas GI symptoms appeared in only a small number of patients.[45] We thus probably underestimate the incidence and severity of small bowel lesions because of the lack of symptoms and means of investigation. Most of our knowledge of intestinal damage during shock is obtained from animal studies, and animal reaction might be different from that of humans. In addition, information obtained from postmortem examination has to be regarded with caution because of rapid autolysis.

Bounous, comparing from the literature different groups of septic, burn, heart failure, hemorrhagic, and postoperative patients with regard to the location of the lesions along the GI tract, found that lesions were most often encountered in the small intestine in all groups of patients except for burn patients, where duodenal location was more frequent.[4]

### Symptomatology

Clinical signs are sometimes so few that they may pass unnoticed. They may vary from mild abdominal distension with diffuse pain to episodes of diarrhea or ileus and trouble of absorption with intolerance to enteral feeding.

### Pathogenesis

***Blood flow.*** The current concept of pathogenesis suggests that redistribution of blood flow from the splanchnic area to vital areas, due to sympathetic response or humoral factor release, leads to perfusion failure of the intestine. However in experiments with hemorrhagic shock, regional blood flow was not severely decreased.[5] In a recent study, splanchnic and hepatic blood flow were measured in post-traumatic patients and were reduced for a few days after injury. A sustained reduction was observed during the first 48 hours even when adequate resuscitation was performed. However, oxygen consumption was maintained by an increase in oxygen extraction.[35]

***Anoxia.*** During ischemic injury, in the experimental animal, the mucosal damage appears first at the villous tip. The opening of extravascular shunting in the villous countercurrent exchanger could be responsible for the anoxia observed at the tip of the villus. Indeed, the villus is supplied by a central arteriole and peripheral venous vessels with opposite directions of flow and a small distance between them so that they function as a countercurrent exchange for oxygen. If the blood flow is decreased or the transit time increased, the efficacy of the countercurrent exchange will increase. Arterial blood will be progressively poorer in oxygen as it reaches the tip of the villus.[41]

***Proteolytic enzymes.*** Local release of proteolytic enzymes may also be of importance. During hypotension there is an increased sensitivity to the digestive action of the intraluminal trypsin and chymotrypsin that can be partially prevented by intraluminal administration of aprotinin or previous pancreatectomy.[6] In addition, the physiologic process by which bile salts and pancreatic elastase produce the loss of brush border glycoproteins of the mucosa may become pathologic when ischemia is present and enhance digestion of the underlying structures.[4] Prefeeding[55] with an elemental diet or saline lavage of the intestinal lumen during or before the ischemia[6] also have a protective effect on the mucosa.

***Oxygen-derived free radicals.*** Recently oxygen-derived free radicals have been implicated in inflammatory disorders and ischemic injury of the small bowel. After transitory ischemia, reperfusion of the small intestine increases intestinal vascular permeability. Several factors have been proposed to be responsible for these changes including histamine, prostaglandins, and endotoxins. However, inhibition of these substances does not prevent the permeability changes. On the other hand, the intravenous administration of SOD and of dimethyl sulfoxide, an OH-scavenging enzyme, almost abolished the ischemia-induced permeability.[37] This suggests a central role for oxygen-derived free radicals in the pathologic process of the reperfusion injury. The xanthine oxidase enzyme has been proposed as the possible source of the superoxide radicals involved in the pathogenesis of the mucosal lesions. This enzyme is very abundant in the mucosal layer of the small bowel, with an increased gradient of activity from the base to the tip of the villus, and from the ileum to the duodenum. Xanthine oxidase is released during ischemia by a calcium-triggered proteolytic attack on xanthine dehydrogenase. Impaired regulation of calcium might thus contribute to the ischemic injury. In cats, the use during the ischemic period of SOD and of allopurinol, a specific inhibitor of xanthine oxidase, has considerably reduced the tissue injury.[73] Other inhibitors of xanthine oxidase such as folic acid and pterin aldehyde administered enterally significantly attenuate the increased vascular permeability induced by reperfusion after ischemia.[38]

## COLON

### Incidence and Clinical Setting

The mucosa of the colon may present localized or confluent dark areas of necrosis similar to those seen in the small bowel. Ischemic colitis, a syndrome where ischemic injury most commonly occurs at the rectosigmoid junction or at the splenic flexure, has been described in critically ill elderly patients with poor cardiac output, congestive heart failure, hemoconcentration with low flow state, or in postoperative conditions after abdominal aneurysectomy. The incidence of ischemic colitis is difficult to determine because many patients do not develop clinical manifestations and it will be discovered only by routine colonoscopy.

### Symptomatology

Initial symptoms may be completely overlooked. Moderate symptoms include diarrhea, occasionally with blood, diffuse abdominal pain, or more often pain localized in the left lower abdomen. Signs of ileus appear later with nausea and vomiting. Leukocytosis is common with eventual fever and chills. Optimizing hemodynamic conditions, bowel decompression, and antibiotic therapy are the common conservative treatments. When only the mucosa and submucosa are involved, the syndrome usually resolves spontaneously. But repeated fiberoptic colonoscopy should be performed to evaluate progression of the ischemia and reach an appropriate surgical decision before gangrene and perforation occur.[102] Measurement of intramucosal pH may offer interesting perspectives in the monitoring of colonic ischemia.[29] Late stricture formation often at the splenic flexure or in the left colon may be the only symptom of ischemic colitis.

### Pathogenesis

***Blood flow.*** Impaired blood supply is commonly considered as responsible for the colonic lesions. The distribution of the lesions at the level of the left colon corresponds to a poorly vascularized sector of the bowel. Intraluminal pressure and bacterial colonization have also been considered as important.[85]

***Proteolytic enzymes.*** Contribution of an enzymatic process to the lesion has also been proposed. In shock, the mucin carbohydrates are degraded by hydrolases produced by human colonic microflora. This could render the mucin glycoproteins susceptible to proteolysis by pancreatic proteases present in the feces and thus contribute to mucosal injury.[99]

***Oxygen-derived free radicals.*** Oxygen-derived free radicals might be responsible for ischemic colonic lesions, as in the small bowel. However, the source of oxygen-derived free radicals is probably not the xanthine oxidase enzyme because its colonic content is low, but rather the aldehyde oxidase enzyme present in abundance in the colonic mucosa.[72]

## PANCREAS

### Incidence and Clinical Setting

Acute pancreatitis may be a quite benign and self-limiting process or a very severe and fulminating disease. Whereas the more benign form is associated with edematous-interstitial pancreatitis, the severe one is usually linked to the necrotizing and hemorrhagic type of pancreatitis. In the critically ill, the development of acute necrotizing pancreatitis results in very high mortality (90 per cent). Not often recognized in multiple organ failure, it seems that in patients dying from shock, signs of pancreatitis are often present at autopsy. Warshaw et al,[101] showed that in patients dying from hypovolemic shock, 9 per cent presented signs of pancreatic injury at autopsy, but with concomitant acute tubular necrosis, this percentage went up to 50 per cent. In patients with prolonged low output after cardiopulmonary bypass, pancreatitis is rarely diagnosed but is fortuitously discovered in 25 per cent of postmortem examinations.[40]

Mortality is not directly caused by pancreatitis itself but by its multisystemic consequences: shock, myocardial depression, respiratory failure, disseminated intravascular coagulation, renal failure, and sepsis. Ranson proposed the use of 11 clinical parameters to assess the severity of the disease.[79]

The pancreas has been implicated in the release of vasoactive substances contributing to hemodynamic instability. A myocardial depressing factor with a negative inotropic effect, also producing splanchnic vasoconstriction and an impaired reticuloendothelial system, was first described by Lefer.[57] Others were unable to confirm the presence of this substance. Although myocardial depression has been confirmed by a low left ventricular stroke work index, it cannot account for the hypotension seen in patients with pancreatitis, but it may compromise appropriate cardiac compensation in the presence of diminished vascular tone. Recently, acute necrotizing pancreatitis was clearly differentiated from the interstitial edematous form by a hyperdynamic circulatory state with low peripheral resistance, high cardiac index, high arteriovenous oxygen difference, and increased pulmonary shunt fraction.[3]

Pulmonary failure is frequent (60 per cent), due to an increase in vascular permeability. In addition, phospholipase A2 released in the systemic circulation probably affects the pulmonary surfactant. Local aggregation of PMN due to the activated complement and the microthrombosis in the microcirculation may be part of the observed dysfunction.

The nonspecificity of the biochemical parameters and the quite atypical clinical presentation in very sick patients with a complex clinical course make the diagnosis of pancreatitis rather difficult. The use of ultrasonography and of computerized tomography may be of some help.

### Pathogenesis

***Blood flow.*** The relationship between shock and pancreatitis suggests that ischemia is one of the causes of pancreatitis.[101] Several studies support the notion that low flow state can aggravate the severity of pancreatitis with progression of pancreatic edema to necrosis.[8] Severe pancreatitis has been induced in dogs by the intra-arterial injection of microspheres.[75] Chemical sympathectomy in rats with acute pancreatitis has resulted in an increase in blood flow and improvement in survival.[20] Systemic hypoxia might also be a factor contributing to the development of pancreatitis.[21]

***Proteolytic enzymes.*** On the other hand, pancreatitis results in marked activation of the proteolytic enzyme system trypsinogen/trypsin, able by itself to activate other enzymes such as phospholipases, elastases, and kinins responsible for autodigestion of the gland. The link between these two etiologic factors, proteolytic enzymes and low flow state, could be through the activation of the complement induced by hypoperfusion and activation of the enzymes.[2] Bile reflux into the pancreatic duct may, of course, also activate the proteolytic enzymes and be a contributory factor.

***Oxygen-derived free radicals.*** Recently, interest has focused on the free oxygen-derived radicals as the common mechanism of injury to pancreatic cells produced experimentally by various types of stimuli (ischemia-reperfusion, partial duct obstruction with secretin stimulation, free fatty acids infusion).[86] The addition of oxygen scavengers to the gland perfusate at the time of the insult prevented or decreased the extent of edematous pancreatitis. In an in vivo study in rats, the delayed administration of oxygen scavenger until after the injury seemed to still be effective in providing protection to the pancreas.[39] Whether an oxygen scavenger offers a solution in necrotizing hemorrhagic pancreatitis has not been investigated.

## BILIARY TRACT

### Incidence and Clinical Setting

Acute cholecystitis has been described after surgery unrelated to the biliary tract, burns, and trauma.[26,67] Extensive surgery, multiple transfusions, and sepsis are considered important risk factors. This form of cholecystitis differs from ordinary cholecystitis by the lack of visualization of gallstones in 22 to 53 per cent of the postoperative patients and even more in trauma patients, and is thus called acalculous cholecystitis.

The lesions in the gallbladder consist of intense injury to blood vessels in the muscularis and the serosa,[34] mucosal ulceration with signs of acute inflammation, and focal necrosis involving all of the gallbladder wall. Although considered as a quite infrequent component of MOF, early identification of the illness is important because of the high mortality associated with delayed diagnosis. Acute acalculous cholecystitis develops 4 to 6 weeks after the surgical procedure or trauma. The diagnosis is often difficult to make because of the masking effect of the postoperative or post-traumatic symptoms. Cholecystectomy is the treatment of choice as the ongoing pathologic process progresses very often to total gangrene and perforation (60 per cent). The mortality rate remains high, between 40 and 70 per cent.[22]

### Pathogenesis

***Blood flow.*** Impairment of the blood supply is suggested by the severe vascular damage observed in the vessels of the muscularis and serosa of the gallbladder. Shock and congestive heart failure decrease blood flow through the cystic artery, the single vessel providing blood to the gallbladder. This may be enhanced by the use of vasoactive drugs like dopamine and epinephrine. Sympathetic response during shock may also constrict the cystic artery. Experimental sympathectomy has been proven to prevent acute cholecystitis in dogs.[47] Glenn et al showed that the histologic findings of acute cholecystitis are similar to those produced in dogs and monkeys by the activation of factor XII Hageman, and proposed that this factor could be the initiating factor of a set of events resulting in vascular damage followed by edema, ischemia, and necrosis of the gallbladder.[34]

***Gallbladder stasis.*** Gallbladder stasis is probably an important factor contributing to the development of cholecystitis. Gallbladder motility may be impaired by bed rest, parenteral nutrition, increased intra-abdominal pressure, and drugs such as narcotics, all conditions frequently simultaneously present in critically ill patients. Often nutrients are withheld from the GI tract of these patients because of oral feeding intolerance and hence, there is no stimulation of cholecystokinin release, which relaxes the sphincter of Oddi and produces the gallbladder contraction. In addition, TPN supplied to these patients results in biliary "sludging" after just 3 weeks of treatment.[65]

***Bile composition.*** Bile composition may be modified and act as a chemical irritating factor due to increased bile salt concentration or bile pigment load from resorbed hematomas. In addition, postoperative dehydration may increase the viscosity of the bile producing a functional obstruction.[33]

***Bile colonization.*** Bacterial proliferation resulting from the stasis of bile may be a superimposed injuring agent of an already injured organ.[23]

## LIVER

The significance of hepatic dysfunction after surgery, trauma, shock, or sepsis has invited the attention of many authors. In some cases the hepatic dysfunction is only biochemically evident, but in other cases patients develop jaundice from the fourth day after injury, followed by a peak at the tenth day, and resolution in uncomplicated cases.[16] This jaundice is associated with elevation of lactic dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Some patients deteriorate due to hepatocellular failure characterized by encephalopathy in stage 4 of the MOF syndrome described by Carrico et al.[13] This stage is often irreversible.

### Clinical Course of Hepatic Dysfunction

***Hepatic response to trauma, surgery, and shock.*** Bywaters in 1946[10] described mild jaundice in 4 patients and microscopic hepatocellular damage in 14 out of 42 severely injured patients. Scott[91] correlated severity of shock with severity of jaundice in the wounded of the Korean war. In the following literature, the post-traumatic hepatic dysfunction was attributed to extensive surgical procedures,[11-76] to massive transfusion with extensive bleeding,[8,9] and to hemolysis and resorption of hematomas.[91] Other suspected factors were hepatic anoxia, anesthesia, drugs, congestive heart failure, and underlying liver disease.[69] The incidence of hepatic dysfunction following major trauma and shock is discussed in other studies and varies from 2 per cent to 81 per cent of all cases of trauma and shock. In 23 trauma patients, following successful resuscitation, the bilirubin peak day was 10.2 ± 2.0, the height of bilirubin peak was 9.5 ± 5.5 mg per cent, the gammaglutamyl transferase values were 59 ± 28 ui, the white blood cell count was 10,800 ± 2,100 per ml, and other values were not significantly different from postsurgical or sepsis jaundice.[16] From liver biopsies taken from 3 hours to 10 days after trauma and shock, the exact nature of the damage seems to be centrolobular congestion, occasionally necrosis with bile stasis.[69]

***Hepatic response to sepsis.*** The incidence of jaundice is low in bacteremic patients (0.6 per cent).[100] Alanine aminotransferase and aspartate aminotransferase are moderately elevated, and bilirubin is between 5 and 10 mg per dl, sometimes reaching 50 mg per cent. Alkaline phosphatase reaches generally twice the normal values, although a marked elevation has been described.[28] Albumin is low.

Liver histology in those cases usually shows intrahepatic cholestasis with or without hepatocyte necrosis. Besides signs of nonspecific hepatitis, Kupffer cell hyperplasia and lymphocyte infiltration in the portal area may be seen. Vermillon[100] described focal necrosis and fatty changes in the parenchymal cells. On electron microscopy, Mekel[96] found signs of cholestasis, and Range[78] demonstrated an increased release of hepatic lysosomal acid phosphatase in the circulation during lactic acidosis. These enzymes and the phacocytized endotoxins could be largely responsible for the progression toward irreversible shock.

Jaundice with sepsis is associated with mortality approaching 90 per cent.[100] However, the pathogenesis of this hepatic disturbance is unknown. In patients with toxic shock syndrome,[36] acute cholestasis was described with a trifold increase in serum bile salt concentration. The role of bile salt has not been studied in other shock or septic states. The respective role of hypoperfusion of the liver, action of staphylococcal exotoxin, and participation of endotoxin in the pathogenesis of the liver dysfunction are discussed in the same study.[36]

## Pathogenesis

If the clinical course of the hepatic response to different stresses is known, its pathogenesis is less understood. Hepatic changes induced by modifications of liver blood flow and oxygenation, by changes in Kupffer cells and the reticuloendothelial system, and by altered metabolism of the hepatocytes will be consecutively discussed.

***Blood flow.*** The liver blood flow usually reaches 800 to 1200 ml per minute and is determined by three parameters: the hepatic arterial vascular resistance, the portal vein flow determined by the vascular resistance of the intestine and the spleen, and the hepatic portal vascular resistance.[81] Arterioportal connections provide functional links between the hepatic arterial system and the portal vein system.

The liver blood flow has an intrinsic and an extrinsic regulation. The intrinsic one is very weak, in particular as far as the portal venous blood flow is concerned, but there is some evidence of hydrodynamic interactions: increase in blood flow in one circuit induces an increase in resistance of the other circuit, resulting in constant liver blood flow. Central venous pressure elevation creates distention of the intrahepatic vessels and decrease of the liver blood flow. This situation is seen in positive pressure mechanical ventilation, right cardiac failure, or pericarditis. In dogs, through liver sympathetic nerve stimulation, 80 per cent of the hepatic volume is emptied to the circulation in 18 seconds.[12] This is achieved by a contraction of the capacitance vessels, and this mechanism is also observed in human beings.

The extrinsic regulation concerns osmolarity, hormones, and drugs. Increase is systemic or portal osmolarity is associated with an increase of portal blood flow, and hepatic arterial and intestinal blood flow. Many critically ill patients have a tendency to be in a hyperosmolar state. Mannitol also increases hepatic arterial perfusion. As far as hormones are concerned, cholecystokinin increases intestinal and, thereby, portal blood flow. Insulin is without effect on the liver perfusion, but glucagon increases total liver blood flow. This "stress hormone"[15] has several actions: it causes intestinal vasodilatation leading to an increased portal blood flow and increased portal resistance, but the most important action of glucagon is its antagonistic effect of vasoconstriction in the hepatic arterial vasculature, neutralizing the effect of anoxia, and increasing the hepatic blood flow.[81] This hormone thus will offer protection from severe sympathetic activity and allow the supply of oxygen necessary for glycogenolysis in the early phase of the shock.

Several hormones are known to be very effective on liver blood flow. Norepinephrine decreases the liver blood flow by inducing vasoconstriction in the hepatic artery and the portal vein, and by decreasing the splanchnic flow. At the same time, systemic artery pressure is increased. Vasopressin at pharmacologic doses is very effective in portal hypertension and bleeding from esophagogastric varices. It produces hepatic artery vasoconstriction, a decrease in portal pressure, and intestinal vasoconstriction.[81] New bedside techniques, such as Doppler flowmetry,[9] are better than the available transhepatic percutaneous procedure for hepatic blood flow measurement. Unfortunately, the portal blood flow in stress has not yet been studied with the Doppler flowmetry.

***Oxygenation.*** In the dog, moderate hypoxemia is deprived of hemodynamic liver effect, but severe hypoxemia ($PO_2$ = 25 mm Hg) increases systemic arterial pressure and reduces hepatic arterial blood flow. Hypercapnia produces a slight increase in hepatic arterial blood flow and a real increase in the portal venous blood flow secondary to mesenteric vasodilation. Hypocapnia reduces arterial and portal venous blood flow.[81] Hypoxemia is one of the main factors of severe impaired hepatic function. It induces an excretory defect, according to the majority of authors.[69,59,24] Portal venous blood flow contributes to 70 per cent of the liver's blood flow and supplies 70 per cent of its oxygen requirements in human beings. The portal venous saturation is 35 per cent. In shock, the portal venous flow decreases significantly and its saturation decreases to 10 per cent. The use of vasopressors will further decrease the liver blood flow.[19]

Very convincing studies[31,44] have demonstrated that adequate oxygenation is more important than the supply of the required liver blood flow. The most hypoxemic region is the centrilobullar cell area, resulting in impaired oxygen uptake, increased lactate production, and also the inability to excrete bilirubin. When $PO_2$ is reduced to a value below 50 mm Hg, the lactate/pyruvate ratio increases in the hepatocytes.[97] The role of oxygen-derived free radicals in liver cell injury seems to be important, too.[72] After ischemia, the liver cell, very rich in xanthine oxidase, will be injured through lipid peroxidation and membrane dysfunction.[17] But in isolated perfused livers of rats, administration of SOD and catalase did not improve postischemic liver function.[63] Further studies have to be conducted to improve our knowledge about this important subject.

***The Reticuloendothelial System (RES).*** The RES is at the center of hepatic dysfunction and pathogenesis in MOF. Several authors have argued that the stage of immunodeficiency predisposes to infectious complications.[84] The liver is a filter of bacteria coming from the GI tract, preventing their passage to the systemic circulation. Pardy[71] demonstrated that blockage of the RES is associated with increased risk of bacteremia. One of the Kupffer's cell functions is the removal of particles from the blood. Their rate of phagocytosis is closely related to the level of circulating opsonins acting as "recognition factors." However, these substances in turn will be deficient in case of Kupffer's cell dysfunction. The magnitude of hepatic blood flow is a limiting factor of the Kupffer's cell capacity. The RES is able to clear endotoxins, microorganisms, activated immune complexes, inert colloids, and clotting factors.[82] In obstructive jaundice, the RES is reduced to 15 per cent of its function and bacteria are found in the lung trapped, but not killed.[52] During the filtering action of the RES, microcirculation thrombosis may occur. Fibrin and platelets produce procoagulant activity, increasing thrombosis and ischemia. When prolonged, these phenomena could result in irreversible organ failure.

***Altered metabolism of the hepatocyte.*** The hepatic oxygen consumption decreases with low systolic pressure (below 60 mm Hg).[105] Concomitantly, cellular AMP and ATP levels decrease, showing mitochondrial oxidation process impairment.[48] However, the ribosomal reprioritization of acute-phase protein synthesis demonstrates the key role of the hepatocyte in the protection of the host tissues from infection and the dead tissue digestion.[93–98] The increase in amino acids, lactate, and glycerol, and also in epinephrine, cortisol, and glucagon increases hepatic glucose production. This phenomen explains, with the insulin resistance, the persistent hyperglycemia in stress.[83] But in late sepsis, hypoglycemia occurs consecutively to liver and muscle glycogen depletion. Liver fat metabolism reactions to stress vary with cause, duration, and intensity of the stress. In early sepsis, there is a fat hypometabolism.[104] In the flow phase, there is an increase in free fatty acid turnover, a decrease in ketone production, and an increase in fat oxidation. Finally, in the extremely ill patient, less fat is oxidized in the liver secondary to low liver blood flow, low oxygen delivery, and low oxygen consumption.[104]

## CONCLUSIONS

The usual criteria for evaluation of GI tract injury in MOF is GI bleeding. However this criteria is imprecise as it develops in severe digestive tract involvement. This explains why GI failure seems to be the least commonly recognized organ failure in MOF. More awareness of this problem and more monitoring parameters should enable the intensivist to create new criteria of GI tract failure in MOF. In view of the poor prognosis of established MOF, the best treatment is obviously prophylaxis by support of organ function and suppression of infection.

The maintenance of GI integrity in MOF seems to be primarily dependent on adequate perfusion and oxygen delivery. With improvement in resuscitative treatment and the possibility of monitoring the GI tract by new techniques, the improved efficacy of treatment should help prevent GI lesions.

General nutritional status should be maintained as well as possible to sustain, in presence of increased protein turnover, the functional reserve of essential organs. An increased exogenous amount of amino acids and calories should be supplied, and this is best achieved by oral feeding. Oral feeding indeed protects from gastric ulceration, enhances the intestinal blood flow, prevents the intraluminal proteolytic aggression of the enzymes, and keeps the biliary tract active. In addition, amino acids delivered to the gut will stimulate protein synthesis in the gut mucosa and in the liver parenchymal and phagocytic cells, whereas amino acids directly delivered to the blood will be more exposed to peripheral catabolism. Oral feeding is an important way to maintain the gut mucosal and liver synthesis capability.[43]

Prevention of infection is essential in the prevention of MOF. Often, the general condition of flu patients suggests infection but the source is not evident. Recently, changes in the GI tract flora have been advocated as the "motor of MOF."[13] According to these authors, the GI tract acts as a reservoir of potent pathogens. Broad-spectrum antibiotic therapy enhances colonization of the GI tract by gram-negative bacilli. Because of the increase in mucosal barrier permeability, these bacteria and endotoxins are able to translocate from the intestine to the peritoneal cavity, the mesenteric lymph nodes, and the portal and systemic circulation. In presence of a decrease in the Kupffer's cell activity and of an acquired immunodeficiency state, these intestinal organisms may be the origin of the often unexplained ongoing sepsis observed in patients with multisystemic failure. The nosocomial pneumonia from gram-negative oropharyngeal flora is a known entity. In the critically ill, it may be the consequence of regurgitation in patients whose bacterial gastric proliferation was produced by the alkaline pH due to the use of antacids or H2-receptor antagonists.[46] Fiddian-Green et al described episodes of infections from intestinal organisms after transient sigmoid ischemia in patients undergoing abdominal aortic operations.[29] As the digestive tract microflora itself forms an important source of infectious complications in already debilitated MOF patients, efforts should be made to decrease colonization resistance. Oral administration of nonresorbable antibiotics has been used, resulting in a decrease in the general infection rate from 81 to 16 per cent and with limited acquisition of new resistant organisms in patients after blunt trauma.[98] Whole gut lavage has been successfully used in inflammatory bowel disease to decrease endotoxemia.[103] Adaptation of this technique to patients at risk for MOF could be of great help in reducing intestinal bacterial proliferation and removing bacterial antigens. Further studies are necessary to verify the practical importance of this form of treatment.

The role of free oxygen-derived radicals in the pathogenesis of lesions at all levels of the GI tract has been demonstrated experimentally in animals. The recognition of a common mechanism of injury by oxygen-derived free radicals may lead to important therapeutic consideration for the future. However, oxygen scavengers in experimental situations were always given before the insult. Whether oxygen scavengers might offer a solution in stopping the ongoing pathologic process remains uncertain and until now has been demonstrated in pancreatitis only. The use of oxygen free radical scavengers has not yet proven its efficacy in clinical situations but might well open a new era in the prevention not only of ischemic injury of the GI tract, but of the general MOF syndrome.

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# Neurologic Complications of Organ System Failure

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Among the various organ systems, the central nervous system (CNS) is unique in the degree of its dependence on glucose and oxygen, and its exquisite sensitivity to their deprivation. Furthermore, it is apparent that the CNS is also sensitive to other, less well defined, derangements in metabolism. Hence, the CNS is secondarily affected by a wide range of disease states (Table 1), and is the target of more exogenous (toxic) substances than other systems.[41] This underlines the importance of treating many of these disorders prior to CNS involvement.

## CARDIAC FAILURE

The mechanisms by which these diverse processes affect the CNS are in some cases quite apparent; in other instances, conjecture and speculation dominate the current literature. Of those conditions in which CNS involvement is intuitively anticipated, cardiac arrest is of great interest to the physician as well as the layman and legislator. This is a common cause of morbidity and mortality in the United States. The issues attending neurologic damage or devastation in the wake of a successful cardiopulmonary resuscitation (CPR) have been brought sharply into focus in recent times by the increasing sophistication of emergency medical services, particularly in and around large urban areas. As a result of this trend, increasing numbers of patients are surviving CPR, but are rendered neurologically compromised.[20] Longstreth et al[46] retrospectively analyzed 459 patients admitted after cardiac arrest and found that 61 per cent eventually regained consciousness. Of these, 33 per cent suffered persistent neurologic compromise, which included cognitive and/or motor deficits. Cerebral (transient global) ischemia is the major consequence of circulatory collapse responsible for this, and is also a common cause of coma in this population.[26,27,65,66]

Protection of neural tissue during, and of neurologic recovery following transient global ischemia is currently an area of great investigational interest as well as intense controversy.[21,23,52,69,70,80] Many of the factors that determine neurologic outcome subsequent to transient global ischemia remain to

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be elucidated, but an obvious contributing factor is the length of time during which a low cerebral blood flow state exists. As predicting neurologic outcome, and if possible, improving it is a critical issue in this setting, Abramson et al[2] analyzed 262 initially comatose cardiac arrest survivors for 1 year as part of an international randomized trial on brain resuscitation. Their findings suggested that when arrest time and CPR time did not exceed 6 and 30 minutes, respectively, 50 per cent of the patients experienced a good neurologic recovery.

Other predictive factors that have been evaluated include awakening time,[46] hypothermia,[67] and style of CPR[11] (closed versus open). Longstreth and his coworkers[46] measured awakening time and reported this to be an important consideration in eventual neurologic outcome. In this study, 25 per cent of those patients who regained consciousness did so by the time they were admitted to the emergency room and 86 per cent within 2 days. Furthermore, their study suggested that the probability of permanent cognitive or motor deficits was directly proportional to the length of coma following cardiac arrest.

The ultimate issue that must be addressed is the definition of a critical level of cerebral blood flow (CBF) that must be maintained in order to meet the metabolic needs of the brain. Different parameters have been defined by various investigators. Heiss,[36] working with animal models, found a CBF at or above 23 ml per 100 gm (brain tissue) per minute is tolerated, whereas when the CBF dimished to 9 ml per 100 gm per minute, infarction invariably resulted (Table 2). Although these appear to be close to human values, many animal models for cerebral infarction remain controversial.[51]

In humans, an average CBF of 55 ml per 100 gm per minute delivering 3 to 5 ml $O_2$ per 100 gm per minute or 45 ml $O_2$ to the whole brain per minute is normal.[17,39,40] However, blood flow is not evenly distributed, since cortical gray matter receives a higher proportional blood flow at the expense of the white matter. Tolerance of the brain to ischemia has been in part defined by intraoperative electroencephalograms (EEG) and evoked potential monitoring during cerebrovascular procedures such as carotid endartectomy, but more work is needed. Until the questions are more completely defined, prediction of neurologic status after CPR shall remain somewhat imprecise.

Obviously, another issue that is critical to this setting is the patient's prearrest physical condition, as well as the cause of the arrest. It seems likely that patients with severe cerebrovascular disease prior to the event will not be tolerant of such an insult. On the other hand, a study by Janati and Erba[37] in children who were victims of near drowning showed this to be a complex pathologic entity whose outcome could not always be predicted from the initial clinical condition or time of submersion.

The clinical examination may be of use in evaluating post arrest patients but may also be misleading. The CT scan can identify areas of infarction, and also may add supportive information to a poor prognosis if a "ground glass" appearance with loss of sulcal pattern as well as definition of gray-white interface is seen. EEG findings of diffuse slow-wave activity also portend a poor prognosis. Electrocerebral silence is the face of normal electrolytes; absent barbiturates and normothermia essentially defines brain-death, but a more complete discussion of this complicated and sensitive topic is beyond the scope of this review.

The prevalence of vascular disease in America affecting both coronary and cerebral circulation mandate that these issues are paramount to any physician in the United States.

**Table 1.** *Some Causes of Metabolic Brain Disease*

- I. Deprivation of oxygen, substrate, or metabolic cofactors
  - A. Hypoxia (interference with oxygen supply to the entire brain—cerebral blood flow normal)
    - 1. Decreased oxygen tension and content of blood
      - Pulmonary disease
      - Alveolar hypoventilation
      - Decreased atmospheric oxygen tension (e.g., high altitude)
    - 2. Decreased oxygen content of blood —normal tension
      - Anemia
      - Carbon monoxide poisoning
      - Methemoglobinemia
  - B. Ischemia (diffuse or widespread multifocal interference with blood supply to brain)
    - 1. Decreased cerebral blood flow resulting from decreased cardiac output
      - Stokes-Adams syndrome, cardiac arrest, cardiac arrhythmias
      - Myocardial infarction
      - Congestive heart failure
      - Aortic stenosis
      - Pulmonary embolism
    - 2. Decreased cerebral blood flow resulting from decreased peripheral resistance in the systemic circulation
      - Syncope: orthostatic, vasovagal
      - Carotid sinus hypersensitivity
      - Low blood volume
    - 3. Decreased cerebral blood flow due to generalized or multifocal increase in cerebrovascular resistance
      - Hyperventilation syndrome
      - Increased blood viscosity (polycythemia, cryo- and macroglobinemia, sickle cell anemia)
      - Bacterial meningitis and encephalitis
      - Subarachnoid hemorrhage
    - 4. Decreased local cerebral blood flow due to widespread small vessel occlusion or tissue necrosis
      - Disseminated intravascular coagulation
      - Systemic lupus erythematosus
      - Subacute bacterial endocarditis
      - Cardiopulmonary bypass
      - Small emboli (fat, fibrin, platelets)
      - Acute viral encephalitis
    - 5. Alterations of blood flow due to failure of autoregulation
      - Hypertensive encephalopathy
  - †C. Hypoglycemia
    - Resulting from exogenous insulin
    - Spontaneous (endogenous insulin, liver disease, etc.)

- II. Diseases of organs other than brain (*Continued*)
  - †B. Hyper- and/or hypofunction of endocrine organs
    - Pituitary
    - Thyroid (myxedema-thyrotoxicosis)
    - Parathyroid (hyper- and hypoparathyroidism)
    - Adrenal (Addison's disease, Cushing's disease, pheo)
    - Pancreas (diabetes, hypoglycemia)
  - C. Other systemic diseases
    - Diabetes
    - Cancer
    - Porphyria
    - Sepsis
- III. Exogenous poisons (see also Ch. 25)
  - A. Sedative drugs
  - B. Acid poisons or poisons with acidic breakdown product
    - Paraldehyde
    - Methyl alcohol
    - Ethylene glycol
  - C. Psychotropic drugs
    - Tricyclic antidepressants and anticholinergic drugs
    - Amphetamines
    - Lithium
    - Phenothiazines
    - LSD-mescaline
    - Monoamine oxidase inhibitors
  - D. Others
    - Penicillin
    - Anticonvulsants
    - Steroids
    - Cardiac glycosides
    - Cimetidine
    - Heavy metals
    - Organic phosphates
    - Cyanide
    - Salicylates
- IV. Abnormalities of fluid, ionic, or acid-based environment
  - A. Water and sodium (hyper- and hypoatremia) (hypo- and hyperosmolality)
  - B. Acidosis (metabolic and respiratory)
  - C. Alkalosis (metabolic and respiratory)
  - D. Magnesium (hyper- and hypomagnesemia)
  - E. Calcium (hyper- and hypocalcemia)
  - F. Phosphorus (hyper- and hypophosphatemia)
  - G. ? Trace metal deficiency or excess
- V. Disordered temperature regulation
  - A. Hypothermia
  - B. Heat stroke, fever
- VI. Infections or inflammation of CNS
  - A. Leptomeningitis
  - B. Encephalitis
  - C. Acute "toxic" encephalopathy
  - D. Parainfectious encephalomyelitis
  - E. Cerebral vasculitis
  - F. Subarachnoid hemorrhage

(*Continued*)

- D. Cofactor deficiency
    - Thiamine (Wernicke's encephalopathy)
    - Niacin
    - Pyridoxine
    - $B_{12}$
    - Folate
- II. Diseases of organs other than brain
    - †A. Diseases of nonendocrine organs
        - Liver (hepatic coma)
        - Kidney (uremic coma)
        - Lung ($CO_2$ narcosis)
        - Pancreases (exocrine pancreatic encephalopathy)
- VII. Miscellaneous diseases of unknown cause
    - A. Seizures and postictal states
    - †B. "Postoperative" delirium
    - C. Concussion
    - D. Acute delirious states
        - Sedative drug withdrawal
        - "Postoperative" delirium
        - Intensive care unit delirium
        - Drug intoxications

*From* Wyngaarden JB and Smith LH: Cecil Textbook of Medicine. Philadelphia, W.B. Saunders Company, 1985; with permission.

†Alone or in combination, the most common causes of delirium seen on medical or surgical wards.

## RENAL FAILURE

Association of CNS dysfunction and renal disease is well established. Acute renal failure (ARF) has been associated with seizures and coma. Uremia encephalopathy is the prominent feature of patients with chronic renal failure (CRF). CNS complications occur with treatment of renal failure, including renal transplantation and hemodialysis. These complications include hemorrhage—subdural, parenchymal (intracerebral), or intraspinal. Dialysis may also result in the dialysis disequilibrium syndrome.

The neurologic manifestations of ARF have been reported in two large series.[19,45] The first sign of dysfunction is a change in mental status progressing first to lethargy, then moving rapidly to disorientation and confusion. If the uremia remains untreated, the patient lapses into coma. In these patients cranial nerve abnormalities occur and may be transient. Diffuse weakness is present and may be associated with fasciculations. Deep tendon reflexes become increasingly hyperactive, resulting in clonus. Papilledema is not a feature of CRF.

EEGs have been studied in patients with ARF.[19,45] The abnormalities include an increase in slow wave (delta) activities and an increase in EEG frequencies above 9Hz and below 5Hz. These changes are unaffected by dialysis but return to normal with recovery of renal function.

A wide range of neurologic abnormalities have been reported with CRF.[4] The patients may develop easy fatigue and sluggishness; a sleep disorder including insomnia and daytime drowsiness; short attention span and difficulty with mental arithmetic. Other problems include restlessness, emotional withdrawal, and irritability. There may be personality changes manifested by paranoid or compulsive behavior. Anxiety, disorientation, confusion, and hallucinations are signs of the encephalopathy. Lastly, there may be transient motor signs manifested as paresis or weakness involving any or all levels.

Patients on dialysis for end-stage renal disease may show evidence of the dialysis disequilibrium syndrome and/or dialysis dementia. The features of dialysis disequilibrium include headache, obtundation, and seizures. Nausea and muscle cramps may also be symptoms. This is a consequence of initiation of dialysis in some patients. Dialysis dementia is a complication of

**Table 2.** *Thresholds of Change in Cerebral Function with Ischemia*†

| | |
|---|---|
| *Cerebral Blood Flow* | *Change in EEG* |
| 50 ml/100 g/min | None |
| 20 ml/100 g/min | EEG amplitude decreases |
| 15 ml/100 g/min | EEG isoelectric |
| *Cerebral Blood Flow* | *Change in Evoked Cortical Responses* |
| 50 ml/100 g/min | None |
| 20 ml/100 g/min | Decreased |
| 15/ml/100 g/min or less | Absent |
| *Cerebral Blood Flow* | *Electrical Activity of Cortical Cells* |
| 50 ml/100 g/min | Normal |
| 18 ml/100 g/min | Absent |
| *Cerebral Blood Flow* | *Fluid and Electrolyte and Metabolic Changes in Ischemic Brain* |
| 50 ml/100 g/min | Normal |
| 20 ml/100 g/min | Intracellular water increases |
| 15 ml/100 g/min | Intracellular water increases. Na/K ratio of brain increases. Adenosine triphosphate and creatinine phosphate reduced to 50 to 70% of normal. |
| 10 ml/100 g/min or less | Failure of membrane ion hemostasis. Membrane depolarized. |
| *Cerebral Blood Flow* | *Cellular Changes* |
| 50 ml/100 g/min | None |
| Below 20 ml/100 g/min | Astrocyte swelling. Swelling of neuronal mitochondria. |
| 10 ml/100 g/min | Increased density of neural perikaryon. Increased electron density of nuclei. |
| 10 ml/100 g/min or less | Random neurons damaged, later all neurons show loss of cellular integrity. Dark staining nuclei, later gross tissue changes occur with softening in infarcted area. Increased extracellular water content. Breakdown of grey and white matter demarcation. Later (weeks) cyst formation. Microscopic evidence of debris clean-up with macrophages. Lipid filled cells and regrowth of capillaries. |

*From* Millikan CH, McDowell F, Easton JD: Stroke. Philadelphia, Lea & Febiger, 1987, p 51; with permission.

†Reductions in cerebral blood flow causing cellular changes are time dependent, and usually, flow reductions that cause cellular change are present for 15 minutes to 2 hours in experimental animals and depend on the particular animal model. Cell changes are also dependent on whether circulation is restored to normal levels and at what perfusion pressure. The values of CBF and the cell changes indicated in this table are based on presumed flow reductions lasting at least 15 to 30 minutes and up to 1 hour.

the treatment of CRF. It is progressive dementia encepholopathy culminating in death.

Structural CNS disorders occur with increased frequency in patients on chronic hemodialysis. Intracranial hemorrhage is the most important consideration. The clinical signs include headache, change in mental status progressing tolethargy, and focal motor signs consisting of hemiparesis. Computerized tomographic (CT) examination will usually reveal a subdural hematoma requiring surgical evaluation to reverse the neurologic signs. Additionally, hemorrhage may occur in the epidural space or parenchymal hemorrhage may occur. Surgical considerations for parenchymal hemorrhage include the size and location of the clot, the general coagulation status of the patient, and consideration of the neurologic status. A small hemorrhage in deep structures in a patient who is improving neurologically may be better managed with consecutive measures to control intracranial pressure. Such measures include head elevation, to facilitate venous drainage and thereby reduce one component controlling intracranial pressure; hyperventilation, to a $PCO_2$ of 25 torr, to maximize venoconstriction and again act on the same intracranial compartment; and intermittent infusion of intravenous bolus Manitol to reduce the overall water content of the intracranial cavity. Manitol infusion has to be closely coordinated with hemodialysis in order to avoid the complication of hemodynamic overload and possible congestive heart failure. Manitol infusion is at times better managed with an intracranial monitor to assess pressure waves.

As is obvious from this discussion, CNS dysfunction is a frequent feature of advanced renal failure. In addition to the neurologic examination, which is quite revealing regarding the functional status of the nervous system, additional tests are of value in classifying the CNS impairment. A CT examination will define structural pathology (that is, clot) secondary to the treatment of renal failure. Additionally, CT evaluation reveals cortical atrophy, a condition usually confined to the elderly, but common in children in CRF.[61,75] EEG abnormalities are usual in patients with uremic encephalopathy (UE) as has been discussed. Cognitive function tests are also useful. The cognitive functions impaired include attention, sustained and selective, short-term memory, and speed of decision making.[71]

The pathophysiology of UE remains poorly defined. Certain factors are known, however. There is no increase in brain water content in CRF; therefore, cerebral edema does not play a role in UE. In animals with ARF or CRF osmolality is increased across brain, CSF, and plasma. This increase correlates with urea concentration. Urea does not account for the entire solute load in CRF. Approximately half of the osmolality increase is due to the presence of undetermined solutes, idiogenic osmoles.[4,10,47]

No correlation exists between the commonly measured chemistries—BUN, creatinine, sodium, chloride, potassium, bicarbonate, and pH—and uremic encephalopathy. Other factors may play a role in the CNS symptoms. Parathyroid hormone has been demonstrated to be elevated in patients with ARF. Plasma and CSF amino acids are altered in CRF and likewise may be an important factor in producing the syndrome.

## HEPATIC FAILURE

Encephalopathy may accompany liver disease. Clinical examples include decompensating chronic liver failure and fulminant hepatic failure. The neurologic manifestations begin with a change in mental status examination. Psychomotor abnormalities are present in a high proportion of patients with cirrhosis. These changes may be identified in the face of an otherwise normal neurologic examination. In addition to mental changes, patients with hepatic encephalopathy show evidence of hyperreflexia as the disease progresses, and extensor toe signs and clonus emerge. Abnormal reflexes including suck, snout, and grasp may be present. Abnormal movements including myoclonus and asterixis are frequently present. Advanced stages of hepatic encephalopathy are associated with abnormal postures including decerebrate and decorticate rigidity.

Asymmetric neurologic findings may be present in hepatic encephalopathy as in other metabolic encephalopathies. Asymmetric signs in liver failure as in uremia should alert one to the possibility of structural abnormality giving rise to the neurologic picture. Structural abnormalities of the CNS once questioned are best investigated with CT or magnetic resonance examination. These may reveal acute or chronic subdural hematoma or other cerebral hemorrhage. Subdural clot evacuation is necessary, either through a craniotomy or with burr holes, depending on the age and liquefaction of the clot. Coagulation defects must be corrected expediently in order to facilitate the operative procedure. Perioperative fresh frozen plasma administration is frequently required and may reduce the incidence of reaccumulation of the hematoma. Intracerebral hematomas are evaluated with the same paradigm as with uremia.

Minor head injury in the face of coagulation abnormalities may be responsible for subdural hematoma collection. The major cause of CNS dysfunction in liver disease, encephalopathy, is less clearly understood. Nitrogenous metabolites derived from the gut that bypass the liver are thought to be partly responsible for the clinical manifestations. Of these, ammonia is regarded as the most important. Others, including mercaptons, phenols, and fatty acids[72,79,83] have been shown to induce coma in animal models. Gamma-aminobutyric acid (GABA) is also produced in the gut and has raised considerable interest as a cause for abnormal neurotransmissions in the CNS, therefore contributing to the encephalopathy. Other neurotransmitter disorders exist in liver failure. The false transmitter octopamine, a beta-hydroxylated derivative of tyrosine, is found in increased concentrations in both the brain and plasma of patients with fulminant hepatic failure.[18,57] There is no clear correlation, however, of octopamine concentration and degree of encephalopathy.

Overall, an increase in permeability of the blood brain barrier (BBB) exists in liver failure.[81] This BBB breakdown may be due to accumulation of toxins derived from the gut. This in turn allows entry of the toxic substances (ammonia, mercaptans, phenols, etc.) into the CNS, as shown in rat studies.[82] Additionally, under these conditions, GABA may cross the BBB in greater amounts. This increase in permeability with all of its ramifications may play a role in the development of encephalopathy in liver failure.

Once hepatic encephalopathy is established, the care is mainly supportive. Attention should be focused on reducing ammonia production in the gastrointestinal tract. A consideration of restricted dietary protein and gut cleansing are helpful. Additionally, all nonessential medication should be discontinued as some may act on the CNS and aggravate the encephalopathy.

## PANCREATIC ENCEPHALOPATHY

In fulminant acute pancreatitis, multiple organ failure occurs, including gastrointestinal hemorrhage, renal failure,[44] respiratory failure,[24] fluid and electrolyte abnormalities, and carbohydrate intolerances. These patients are also subject to disordered nitrogen metabolism.[33] These metabolic abnormalities, along with hypoxia, which is also frequently seen in acute pancreatitis, may together ultimately result in encephalopathy. This may manifest itself clinically in a wide spectrum, ranging from acute delerium, through agitated stupor and seizures to coma. This is usually seen between the second and fifth day of onset of pancreatitis.[64] The pathogenesis of this rather ill-defined syndrome remains unclear[34]; this may represent the effects of the combined metabolic insults. Alternatively, it could be the result of the influence on the CNS of factors released by the necrotic pancreatic tissue. Vogel has shown that lipase is capable of destroying myelin and may play a role in this condition.[76] Pathologic lesions in the CNS include focal areas of capillary hemorrhage, perivascular edema, and reactive gliosis. The hemorrhages were most frequently observed in the basal ganglia and periventricular regions.[58] Areas of demyelination and infarction with necrosis and myelinization of capillary vessel wall, as well as central pontine myelinolysis have also been noted.[76]

Treatment is directed toward correcting the metabolic disturbances and other complications of the primary process. Of course, seizures should be controlled, should they occur. This condition, if in fact it is a separate entity and not an epiphenomenon, will require further investigation so that its prognostic implications and treatment, if any, can be better defined.

## ENCEPHALOPATHY COMPLICATING PREGNANCY

It is estimated that hypertension will attend 5 to 10 per cent of all pregnancies.[55] Encephalopathy represents the extreme end of a spectrum of organ dysfunction that can occur in the face of the hypertensive gravid patient. A variety of names, including pre-ectomysia, ectomysia syndrome, gestosis, toxemia, and many others[15] have been ascribed to this condition. This devastating but fortunately rare condition continues to frustrate physicians. A large number of theories have been advanced insofar as etiology is concerned. None have as yet gained universal acceptance.[16] The striking preponderance of instances of this syndrome in primagravida patients attracts attention, but offers no clues. Of greater interest is its failure to recur in subsequent pregnancies in those who survived the initial assault. The most common causes of death are heart failure and cerebral hemorrhage.

Cerebral hemorrhages include petechial hemorrhage in cortex and subcortical areas, as well as areas of ischemia infarct. Massive cerebral hemorrhage can also occur. Cerebral hemorrhage is often found in patients who die within 2 days of the onset of failure.

Aseptic sagittal sinus thrombosis can also occur. Again, although many theories exist, the reasons for the specific pathologic changes, or an explanation for the exact cause of the seizures, is yet to be forthcoming.

These patients should be managed by personnel acquainted with this disorder, and in a setting where close monitoring can be conducted. Since the only definitive treatment is termination of the pregnancy, the considerations are complex and beyond the scope of the purely medical. Appropriate consultations, including internists, nephrologists, neurologists, and neurosurgeons should be referred to rapidly when indicated. The prognosis remains guarded for those who actually develop seizures, with a worldwide perinatal mortality as high as 35 per cent.[84]

## ENDOCRINOLOGIC DISORDERS AND ABNORMALITIES OF FLUIDS AND ELECTROLYTES

As previously mentioned, the CNS is remarkably sensitive to changes in electrolyte and trace metal concentration, osmolarity, glucose, and other metabolites, as well as acid/base balance. Numerous metabolic derangements resulting from dysfunction of the endocrine system can result in encephalopathy.

### Hyperglycemia

Ketoacidosis represents an uncontrolled production of free fatty acids in association with massive glyconeogenesis. This stimulates ongoing osmotic diuresis, often in association with vomiting and anorexia. The characteristic picture that develops is well known to clinicians: a significantly dehydrated, acidotic patient who generally has an altered sensorium and may be in coma; Kussmalil breathing and the classic "acetone" odor often also attend the situation. The diagnosis is often further supported by a history of recent infection, surgery, intercurrent myocardial infarction, or other physiologic stress in a known diabetic. What is particularly critical is that the diagnosis be entertained in the absence of a supporting history. The diagnosis should be considered in any patient presenting to the emergency room in undiagnosed coma.

The effects of hyperglycemia on the brain require further study. In one study by Fulop et al, depression of neurologic status was correlated with extracellular hyperosmolarity, but not with hyperglycemia or pH of blood or CSF.[29] Whether cerebral dehydration or edema results remains controversial.[5,49,53] Whether the so-called "idiogenic osmoles" are actually generated in human brain under these circumstances remains to be established.[30] Since ketoacidosis represents a vast overall metabolic disturbance, other factors that have not yet been considered may also contribute to the overall picture. Laboratory evaluation will readily confirm the diagnosis, with serum glucose elevated to 300 to 400 mg% or more.

The management of ketoacidosis rests on repletion of the vascular space in conjunction with insulin therapy to control hyperglycemia. Electrolyte abnormalities must, obviously, be corrected as well. These patients require an intensive care setting with aggressive management, but this approach will often produce gratifying results.

Nonketotic hyperosmolar coma was first recognized in 1957 by Sament and Schwartz[60] and is now accepted as significantly different in its pathogenesis and presentation from ketoacidosis. This is generally thought to occur in elderly patients who are noninsulin dependent diabetics (type II). The history is usually that of several days of progressive lethargy, often culminating in a coma. Neurologic examination may or may not be focal, but (in contrast to diabetic ketoacidosis) seizures can be seen in 10 to 15 per cent of these patients.[56] Again, in contradistinction to diabetic ketoacidosis, the serum glucose in nonketotic coma is extremely high, frequently exceeding 1000 mg%.

The cornerstone of therapy is rehydration. This, usually without insulin or other intervention, will correct the imbalance and result in clinical improvement.[32] However, the mortality and morbidity of hyperosmolar coma is probably higher than that of ketoacidosis, although the incidence appears to be less.[14]

Again many of the same factors that were considered in the pathogenesis of ketoacidosis are probably at play in nonketotic hyperosmolar coma. Significant differences also exist. While some of the electrolyte imbalances are analagous, hypoerosmolar coma patients are not as profoundly acidotic as those afflicted with ketoacidosis. Moreover, there is not the massive rapid matabolic assault that occurs with ketoacidosis. Of course, it is well known to seasoned clinicians that it is that same assault that brings those with ketoacidosis to medical attention more expediently, thus improving their outcome.[8] In hyperosmolar coma, on the other hand, the process develops insidiously over days, thus allowiing for these patients to become much more dehydrated than those with ketoacidosis. This more gradual development of hyperosmolar coma may well change the characteristics of the way the brain deals with the entire process, and is perhaps responsible for the poorer prognosis in this entity. Another factor that may contribute to this is the fact that the population vulnerable to this process is an elderly population who may already have cerebrovascular disease. The hyperosmolar state probably further compromises cerebral blood flow, thus setting conditions for potential cerebrovascular accident. The increased glucose is, of course, an unfavorable setting for ischemic brain. How alterations in the electrolytic composition of the local milieu would further compromise cerebral tissue is not clear at this time. Obviously, CNS cells are permeable to water, which probably leaves cells in hyperosmolar state. However, it seems unlikely that fluid shifts could account for the entire picture. The normal concentrations in the cerebral cortex of various species are $Na^+$ (50 to 60 mmol per kg), $K^+$ (85 to 100 mmol per kg), $Cl^-$ (35 to 45 mmol per kg), $CA^{2+}$ (1 to 2.8 mmol per kg), $Mg^{2+}$ (5 to 6 mmol per kg), and $HCO_3^-$ (10 to 20 mmol per kg).[9] Balance is provided by intracellular anions in the form of macromolecular proteins. How much these change in the hyperosmolar state is not known. Others believe the total body $Na^+$ deficit is instrumental in causing disordered CNS function. It is not known whether the shifts in electrolytes that obtain in either ketoacidosis or nonketotic hyperosmolar coma affect this milieu. There is evidence that the brain can adapt to a hyperosmolar state,[6] but confirmation is pending. One mechanism by which this is thought to occur is the development of additional solute particles, rather than simple water loss. These have been called the "idiogenic osmoles" alluded to previously.[9] Whether such a species actually exists and, if so, if this provides protection to the brain or wreaks further devastation will all require vigorous investigation. The fact that seizures occur in hyperosmolar coma but not in ketoacidosis raises other questions concerning cerebral metabolism. While it would seem intuitive that such metabolic derangements should result in CNS dysfunction, the mechanisms accounting for the dysfunction remain to be elucidated.

### Hypernatremia

Hypernatremia is also prominent in both of these disorders, as well as a host of renal, endocrinologic, CNS, and other conditions. This condition can be seen in diabetes insipidus, as well as Conn's syndrome and Cushing's syndrome. These patients frequently experience neurologic symptoms, including lethargy, muscle weakness, and an encephalopathic picture. Untreated, this condition can progress to coma, and it is well known that this condition has a high mortality in children. Treatment begins with fluid restriction, but the rationale must be guided by the primary process. Often, endocrinologic manipulation can be helpful.

Again, the mechanisms responsible for the development of an encephalopathic picture in this setting are not known; it is presumed, however, that they have to do with fluid and electrolyte shifts. Since neuron-to-neuron communications (synapse) occur via electrolyte exchange, this would appear to be plausible. In an attempt to further describe the dysfunction in electrical terms, the EEGs of experimental animals in which hyperosmolarity had been induced were studied.[68] Changes noted included a disappearance of fast activity and progressive slowing of background frequencies. Although adults with hypernatremia generally have normal EEGs, in a study of hypernatremic children, 10 of 52 were found to have similar EEG changes. In both the experimental animals and the children, the changes resolved with correction of the electrolyte abnormality.[13]

### Hyponatremia

Bearing in mind the critical role of electrolytes in the excitability of membranes, it becomes obvious that hyponatremia, like hypernatremia, must involve the neurologic system. In fact, hyponatremia is often regarded as the most common electrolyte abnormality encountered in the clinical setting in the United States. As with hypernatremia, the causes of hyponatremia are myriad; they generally reflect a dilutional disorder, rather than a significant diminution in total body sodium. Consequently, hyponatremia is often regarded as water intoxication. The most common cause of chronic hyponatremia is probably the syndrome of inappropriate antidiuretic hormone (SIADH), which occurs in a variety of clinical settings. Hyponatremia is also seen in cardiac, hepatic, and renal failure, as well as in a number of other settings. In the hospitalized population, indiscriminate use of intravenous fluids is clearly a common cause of transient hyponatremia.

Hyponatremia frequently announces itself with CNS symptomatology. Patients may experience headaches, weakness, lethargy, confusion, delerium, hallucinations, muscular twitchings, and seizures. Untreated, the condition can progress to coma and death. More important than the absolute serum level of $Na^+$ is the rate at which the level declines. This is well known to clinicians and has also been shown to be true in an animal model. Rabbits rendered hyponatremic over a 2- to 3-hour period sustained a high incidence of mortality, whereas animals in which the same serum $Na^+$ level was achieved over several days frequently demonstrated no evidence of CNS dysfunction.[7]

Pathologically, the main CNS effect of the hyposmotic state is cerebral swelling and edema. However, the brain appears to compensate for this in some way; the cerebral water content is less than would be expected merely on the basis of calculating osmotic equilibrium.[59] The mechanism responsible appears to act through the loss of osmotically active particles, such as sodium, glucose, and amino acids.[59,73] This is reminiscent of the mechanism functioning in hyperosmolar states; whether these phenomena represent different functions of the same mechanism functioning in hyperosmolar states or different functions of the same cytosystem remains to be seen. It is also thought that the CNS may be further protected in hypoosmolar states by means of a mechanism that increases bulk flow in the CSF, thus decreasing cerebral water content.[50]

Other than cerebral edema, as mentioned previously, there are no lesions that are characteristic or diagnostic of hyponatremia.[78] Central pontine myelinolysis has been associated with hyponatremia, but the relationship between these two phenomena is not clearly understood. Some investigators feel that the mixture of gray and white matter in the pons predisposes this area to such lesions.[54]

How swelling affects the function of the CNS is not clear at this time. The increased intracranial pressure probably has the same deleterious effects in hyponatremia as it does when it occurs with other etiologies, but it does not appear to be the primary problem in this state. Brain herniation is not commonly reported. It is conceptually attractive to therorize that the electrolyte imbalance affects the cell membrane systems responsible for electrolytic exchange during depolarization (such as $Na^+/K^+$ATPase). Others have postulated an effect on neurotransmitter or amino acids responsible for brain metabolism and synoptic activity.[43,64] Although theories abound and many investigators have already made substantial contributions toward understanding the effects of electrolytic disorders on CNS, the answers have not yet been found.

Clinically, the key to management of the patient with hyponatremia is a matter of addressing the causes directly, in association with judicial fluid restriction. Often this course of action will result in complete resolution of the problem. Avoidance of too rapid a correction of electrolyte imbalances must also be weighed into the therapeutic algorithm. Therefore, more drastic measures, such as diuresis or hypertonic saline, should be reserved for certain selected clinical situations.

## Disorders of Calcium Metabolism

In recent years, calcium has gained increasing attention from both the clinician and the investigator, for several reasons. First, new physiologic roles continue to be assigned to this cation, as techniques for performing in vitro and in vivo neurophysiologic testing continue to improve. In addition to well-known roles in bone, muscle, and hematologic metabolism, $Ca^{++}$ is now known to be important in vascular and neurophysiology. It is also important in the function of cell membrane ATPase, as well as intracellularly via cAMP and calmodulin systems. Also, with the introduction of calcium channel blockers, clinicians have become more curious about possible therapeutic intervention in states of disordered calcium metabolism.

Calcium is maintained within a fairly narrow physiologic range by a complex system of homeostasis that includes parathyroid hormone, vitamin D, and probably calcitonin.[12] Hypercalcemia is now recognized to be more common than was once suspected.[62] The most frequent cause of increased serum calcium is neoplasis; other causes include hyperparathyroidism, vitamin D intoxication, sarcoid, milk-alkali syndrome, adrenal insufficiency, thyrotoxicosis, thiazide diuretics, chronic immobilization, and in-dialysis accidents.[12] The clinical presentation frequently relates to the underlying cause, but neurologic symptoms including vomiting, lethargy, confusion, delerium, psychosis, and coma are not uncommon. If intracranial pressure (ICP) occurs, an abnormal EEG with slowing and nonspecific changes can be seen. Occasionally, this can be a life-threatening situation. Management includes intravenous hydration with saline as a critical first step. Diuretics, steroids, or other measures may be required, contingent on the underlying cause.

The cause of neurologic manifestations in the setting of hypercalcemia is also subject to speculation. No specific pathologic changes have been identified.[54] Interestingly, there is usually little change in the CSF concentration of $Ca^{++}$ if the plasma level is altered by $Ca^{+2}$ infusion, parathyroid hormone administraton, EDTa, uremia, or vitamin D intoxication.[38] This is, for instance, in contradistinction to $Na^+$, in which fluctuations in the CSF generally parallel those in plasma. As in other instances previously mentioned, a consideration in hypercalcemia is that there is a disturbance in the manner in which ions distribute themselves along cellular membranes. This needs to be investigated further, as do the possible roles of $Ca^{+2}$-dependent cytosolic activities, such as cAMP.

Hypocalcemia may be seen in renal disease, vitamin D deficiency, hypoparathyroidism, pancreatitis, and malnutrition. CNS involvement includes increased intracranial pressure and, at times, calcification of the basal ganglia and dentate nucleus of the cerebellum. Signs and symptoms include hyperexcitability, seizures, confusion, hallucinations, delerium, and obtundation. Coma is uncommon. Occasionally, there may be extrapyramidal signs, but a relationship with the basal ganglia calcifications has not been causally established.[54] Peripheral neuropathies may also be seen. Treatment includes $Ca^{++}$ and attention to the primary process.

**Trace Element Abnormalities**

Other electrolyte changes that occasionally induce CNS manifestations include disorders of magnesium and phosphates. Decreased levels of either of these can lead to apprehension, anxiety, psychosis, or seizures.[25,31] No specific pathologic changes occur in these entities. Hypermagnesemia, on the other hand, has well-known sedative effects. This is rarely a cause of clinical concern, except in CRF. In that setting, hypermagnesemia tends to be iatrogenic in origin. Of interest in the discussion of fluid, electrolyte, and acid-base effects on CNS is the fact that metabolic acidosis itself is not thought to cause significant havoc in the CNS. In states such as uremia, cholera, or hypercapnia, acidosis per se is usually not associated with coma. Infusion or ingestion of acid sufficient to induce acidemia will not cause coma in animal models or human subjects.[3] At present, the relationships of plasma, CSF, pH, and brain intracellular pH are yet to be defined. It would seem logical that significant brain intracellular pH should produce abnormalities of the cytosolic machinery, but this has not yet been definitively established.

## ADRENAL AND THYROID DYSFUNCTION

Other endocrinologic disorders that are occsasionally associated with CNS dysfunction include adrenal and thyroid abnormalities. Adrenal insufficiency (Addison's disease) can arise from a variety of causes, and generally presents as a slow, insidious process. However, an acute crisis of psychosis, delerium, or even coma can punctuate the course. Cerebral edema is generally the only pathologic finding, and the neurologic findings are generally considered to be caused by disordered electrolyte and water metabolism. Occasionally, these patients may also develop panesthesias and/or flaccid paralysis. This may be due to myelopathy[48] or polyradiculopathy.[1] On the other hand, in Cushing's disease, the neuropsychiatric manifestations (mainly depression but occasionally psychosis) are thought to be due to effects of the increased steroid burden. No specific neuropathology changes are consistently seen. It should be noted that these patients have an increased incidence of hypertension and therefore a proportionately higher incidence of ischemia or hemorrhagic infarcts at autopsy.

Patients suffering from thryoid abnormalities may also experience CNS symptoms. Thyroxine and triiodothyronine are known to generally increase the body metabolism dramatically. In addition, they have been shown to increase brain excitability, enhance the capacity to support electroshock seizures, and shorten postictal depression.[74] The same investigators found evidence that thryoid hormones affect the distribution of electrolytes within neurons. Other work has suggested that alterations of neurotransmitters occur in the face of thyroid stimulation. The "sympathetic" nervous system overdrive, which seems to occur in hyperthyroid patients, is well known to clinicians. Hyperthyroid patients were found to have decreased levels of CSF homovanillac acid, suggesting an alteration in dopamine metabolism.[42] Hence, the CNS manifestations of altered thyroid metabolism can be easily seen. In hyperthyroid states, CNS manifestations include insomnia, irritability, personality changes, and occasionally seizures. The syndromes of hyperthyroid chorea, acute thyrotoxic encephalopathy, and thyroid storm are also known. In hyperthyroid chorea, increased sympathetic tone and other findings of hyperthyroidism are combined with choreiform movements. Treatment includes antithyroid medications and dopamine antagonists, which usually reverse the movements.[35] Thyrotoxic encephalopathy, as described by Wadenstrom,[77] consists of acute bulbar manifestations and paralysis of the pharyngeal musculature; lower conial nerves may be involved and coma may occur. This may be part of a spectrum with thyroid storm, in which massive excesses of thyroid hormones can lead to hemodynamic instability as well as coma. There are no CNS pathologic changes that characterize these disorders.

Hypothyroidism, on the other hand, slows metabolism and, if congenital, will retard the growth of the CNS. In this case, demonstrable changes in the CNS include cerebral hypoplasia, vascular abnormalities, and decreased brain weight.[28] This can lead to psychomotor retardation, deafness, and other signs.

Patients who suffer adult onset of hypothyroidism can also experience CNS changes, including delusions, memory deficits, lethargy, and hallucinations.[81] Coma is uncommon, occurring in less than 1 per cent of hypothyroid patients. There may be accumulation of interstitial fluid, but again there are no pathologic changes.

## SUMMARY

Neurologic manifestations of organ failure are common and occasionally represent a major portion of the morbidity associated with the primary illness. Largely, the neurologic sequelae can be divided into three groups. The first group includes metabolic disorders and is mainly manifested by encephalopathy. Encephalopathy crosses organ systems in terms of primary disease processes, and the underlying mechanism is as yet unresolved. The second group is related to structural abnormalities, mainly hemorrhage, due to hematologic or coagulation defects secondary to the primary illness. These lesions will frequently require surgical intervention with subsequent resolution of the neurologic signs. The third category consists of cerebral ischemia either regional or global. Symptoms and signs correlate well with the time interval and location of the ischemia. Therapy is directed toward reducing ischemic time, thereby reducing morbidity.

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# Modifying Systemic Responses with Anesthetic Techniques

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Sepsis, elective surgery, and traumatic injury all result in major alterations in systemic functions. This so-called response to stress is characterized by significant changes in hemodynamic, respiratory, immunologic, and biochemical parameters. The anesthesiologist and critical care specialist frequently must deal with the consequences of this response. This article will initially review the effects of various anesthetic agents and techniques on the response to elective surgery and then discuss whether and how these observations can be applied to patients with multisystem organ failure.

## THE RESPONSE TO SURGICAL INJURY

The response to surgical injury, which has been discussed in more detail elsewhere in the issue, has traditionally been viewed as consisting of activation of the endocrine system, with a shift to a predominant counter-regulatory hormonal (glucagon, cortisol, and catecholamine) mileu.[104,120] More recently it has been recognized that the immunologic system also plays a major role in mediating this response.[44,60]

The production of a wound, either surgical or traumatic, evokes reproducible metabolic, hormonal, and hemodynamic changes in body functions. The response can be separated into two phases, an initial "ebb" or shock phase lasting about 24 to 48 hours followed by a "flow" or catabolic phase.[39] The "ebb phase" responses include high levels of circulating catecholamines,[56,91] suppression of insulin secretion,[66] and elevated cortisol,[96] glucagon,[99] adrenocorticotropic hormone (ACTH),[33] growth hormone,[47] beta-endorphin,[46] and interleukin I.[6] There is often an increase in the glucagon to insulin ratio.[31] These changes are associated with hyperglycemia,[2,115] increased protein[4,39] and fat[2,115] mobilization, enhanced gluconeogenesis,[108] and sodium and water retention.[12] The magnitude of the changes is roughly proportional to the extent of the surgical trauma.[123] Evidence points to synergism between the "counter-regulatory" hormones: cortisol, glucagon, and the catecholamines.[101,104]

The subsequent catabolic or "flow" phase is also characterized by increased fat[58,115] and protein[65,76] mobilization, increased gluconeogenesis,[64] and retention of sodium and water.[7] Metabolic rate increases,[73,77] catecholamine secretion remains elevated,[40] nitrogen balance is negative, and serum cortisol, glucagon, and growth hormone levels remain elevated. Hyperglycemia is present despite increased levels of circulating insulin. This is thought by some to be due to impaired insulin release and insulin insensitivity at the cellular level,[13] and to an increase in gluconeogenesis.[104] After elective surgery, with an uncomplicated convalescence, there is a progressive return to baseline metabolic conditions.

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The metabolic response to stress is thus biphasic with the initial phase dominated by massive catecholamine release and a subsequent one by steroid and peptide hormones.[8]

The metabolic response to surgery is thought to be mediated by a neural mechanism[63,69] and possibly also by neurohumoral mediators.[5] Evidence for the former comes from the work of Hume and coworkers[65] who demonstrated that division of afferent fibers from the area of the injury suppresses the adrenocortical response. Additional evidence is provided by the observations that epidural anesthesia[69,71] and high doses of centrally acting narcotics[53,117] produce similar suppression.

There has been increasing recognition of the importance of the immunological system in the response to stress. Lymphocytes infected with New Castle disease virus synthesize immunoreactive ACTH and endorphins[14] while monocytes produce interleukin (IL)-I and hepatocyte stimulating factor which stimulate pituitary cells to release ACTH.[122] IL-I,[44] also known as endogenous pyrogen, activates T-lymphocytes during antigen presentation by inducing IL-2 receptor formation as well as IL-2 production,[79,114] induces hepatocytes to produce acute phase reactants,[44] increases endothelial adhesiveness for monocytes, induces proteolysis, causes fever, and induces hemopoetic stem cells to become responsive to granulocyte and granulocyte-monocyte colony stimulating factor, thus inducing leukocytosis.[30] Beutler and coworkers[9,11] observed that a glycoprotein excreted by endotoxin-stimulated macrophages, cachectin/tumor necrosis factor, causes distributive shock,[110] inhibits lipogenic enzymes in vitro, and stimulates IL-I production.[10,109]

## ANESTHETIC MODIFICATION OF THE SYSTEMIC RESPONSES TO ELECTIVE SURGERY

The mechanisms that trigger the cascade of events leading to the responses to surgical injury are multiple. Nocioceptive afferent neural receptors located in the area of injury alert the brain to initiate neurohumoral responses, while the components of the immunologic system in the area of injury also initiate a series of events that contribute to the observed homeostatic alterations. The ability of general anesthetic agents to suppress central nervous system function, and the ability of the regional anesthetic techniques to block afferent stimuli, have stimulated many investigators to examine the effects of various anesthetic techniques on the responses to elective surgery.

### Epidural Anesthesia/Analgesia

The introduction of local anesthetics into the epidural space allows for the selective and continual neural blockade of afferent and efferent stimuli. This technique is frequently used for intraoperative anesthesia and postoperative analgesia. Kehlet[70] and others[36] have clearly and repeatedly demonstrated that epidural anesthesia encompassing all the afferent pathways from the surgical field may significantly modify the endocrine responses to lower abdominal surgery and operations on the lower extremities. In a series of studies comparing the effects of inhalation anesthesia (halothane and nitrous oxide) with epidural neural blockade ($S_5$ to $T_4$) using bupivicaine, Kehlet and his colleagues demonstrated significant differences in the response to abdominal hysterectomy.[70] They noted intraoperative attenuation, during epidural anesthesia, of the increases in plasma catecholamines,[49] aldosterone,[21] cortisol,[36,48,54] renin,[38] growth hormone,[38] prolactin,[38] and antidiuretic hormone. However, plasma levels of thyroid hormones,[18] glucagon,[17] and insulin[17] were only minimally affected. This resulted in preservation of normoglycemia,[17] decreased postoperative nitrogen losses,[20] and diminished postoperative oxygen consumption,[70] as well as less postoperative pain.[87] It is interesting to note that, in the epidural group, normoglycemia was maintained despite no increase in insulin or C-peptide levels, thus suggesting decreased glucose production (gluconeogenesis).[19] Although 8 hours after surgery had begun, glucose levels were lower in patients receiving epidural analgesia than those who had received general anesthesia, there was no difference between the two groups in both the glycemic and insulin responses to an intravenous glucose tolerance test.[25] This likely is a reflection of the abnormal hormonal mileu that includes sufficient levels of cortisol and catecholamines to alter the response to a glucose load, but that is sufficiently attenuated by the epidural analgesia to prevent a rise in serum glucose.[25] Injury (total hip replacement under general anesthesia) produces a characteristic change in intracellular (muscle) amino acid concentrations.[86] The branched chain and aromatic amino acids along with methionine are increased while glutamine is strikingly decreased. After hip replacement using epidural anesthesia analgesia, Christensen and colleagues[29] observed no change in the muscle amino acid pattern. It is still unclear whether extradural anesthesia results in a more negative sodium balance.[12] It is important to note that in the majority of the studies cited above, the epidural analgesia was continued for 24 hours postoperatively, while in patients receiving general anesthesia, postoperative pain medication consisted of intermittent doses of intramuscular narcotics. Also, in many of the studies the degree of attenuation of hormones, such as cortisol by epidural anesthetics, decreased after surgery. The mechanism of attenuation of the stress response after lower abdominal surgery in patients given epidural analgesia is thought to be blockade of the afferent input; the higher the level of the blockade, the more extensive the attenuation. This was demonstrated by Engquist and coworkers[48] who demonstrated that blockade of $T_4$-$S_{4\text{-}5}$ was more effective than that of $T_8$-$S_{4\text{-}5}$.

The use of a combination of general and epidural anesthesia has also been the subject of much investigation. Engquist and colleagues[48] observed higher plasma cortisol levels in patients receiving thoraco-lumber epidural anesthesia plus general anesthesia (enflurane and nitrous oxide) than those receiving only the epidural anesthesia. A likely reason for this difference is that the inhalational agents are unable to attenuate the stimulation of the endotracheal tube, thus resulting in a greater response in patients treated with a combined technique. Moller and coworkers[88] addressed the question of whether the stress response already initiated by surgical trauma was affected by starting epidural blockade 30 minutes after the start of surgery and general anesthesia. They demonstrated that epidural blockade with bupivacaine could prevent further increase in glucose and cortisol but could not effect a return to the levels seen with epidural analgesia begun prior to surgery. The authors concluded that once initiated, the endocrine response to surgical trauma is self-perpetuating, but that subsequent blockade may prevent a further increase in the responses.

Subarachnoid blockade with local anesthetics can suppress the metabolic responses to abdominal hysterectomy in a fashion similar to that found with lumbar epidural anesthesia.[89] In patients receiving hypobaric subarachnoid blockade for hip arthroplasty, Davis and colleagues[41] observed almost no rise in glucose or cortisol immediately after surgery, unlike patients who received general anesthesia. Similar observations, including suppressed catecholamine secretion, have been observed by others[94] during perineal and lower extremity surgery performed under subarachnoid blockade. It appears that subarachnoid blockade, like epidural blockade, can alter neural input and thus attenuate neurohumoral output to lower abdominal and lower extremity surgery.

The ability of epidural anesthesia with local anesthetics to suppress the metabolic responses during upper abdominal surgery is an active area of investigation. Some studies have demonstrated attenuation, but not total inhibition, of the cortisol increase,[3,112,113] while other studies have failed to do so.[22,111] The failure to affect cortisol secretion was attributed by some investigators to intraoperative vagal stimulation,[22] but intraoperative local anesthetic blockade of the vagus nerve in patients given thoracic epidural local anesthetics failed to attenuate the hormonal response.[111,113] In these studies however, there were significantly smaller increases in blood glucose during epidural anesthesia than during general anesthesia.[3,22,111-113] In a more recent series of studies, Rutberg and coworkers[54a] noted that patients undergoing cholecystectomy with general anesthesia (fentanyl plus nitrous oxide) alone had higher levels of norepinephrine and epinephrine than did patients receiving general anesthesia plus an extensive extradural block ($S_5$ to $T_4$) with bupivacaine. It is important to note that there was no substantial inhibition of the increase in plasma cortisol concentration although the increase was significantly less pronounced than when general anesthesia alone was given. Blood glucose and free fatty acids were significantly lower 2 and 4 hours after skin incision in the group that received epidural local anesthesia; glycerol and lactate followed similar patterns. This pattern is consistent with the observations of Kehlet in hysterectomy patients[71] and Asoh and colleagues[3] in upper abdominal surgery; it is in contrast to the results of Traynor and coworkers.[111] Arterial alanine and insulin concentrations were unaffected by the different types of anesthesia[55] in a study by Hakanson and colleagues, although Lund and coworkers[82] observed lower insulin levels in patients given general anesthesia plus regional anesthesia than those given only general anesthesia. The reason for the smaller increase in glucose concentration in patients given general plus thoracic-lumbar epidural anesthesia was examined by Lund's group.[82] The increase in glucose during stress is attributed to both an increase in production (gluconeogenesis) of glucose and a decrease in peripheral utilization (insulin intolerance). The results of the hepatic vein catheterization studies by Lund[82] appear to point to both a lesser net hepatic glucose production in patients receiving both general and epidural anesthesia and an increase in peripheral glucose uptake. Splanchnic uptake of glycerol was lower in the extradural group, indicating a decrease in the lipolytic response to surgery. Lund and colleagues[83] also examined the splanchnic exchange of amino acids (the uptake of amino acids is accelerated in the postoperative period) and found no difference between cholecystectomy patients given general anesthesia alone and those also given thoracic epidural analgesia. It appears that after upper abdominal surgery there is little difference in amino acid metabolism between the two anesthetic techniques. This is consistent with the observation of Seeling and coworkers[103] who observed no difference in nitrogen balance in patients who had undergone abdominal and abdominal-thoracic procedures between those given 4 days of continuous epidural analgesia with 0.2 per cent bupivacaine and those given intermittent intramuscular postoperative narcotic analgesia. The ability to suppress the endocrine-metabolic response to stress using epidural local anesthetics is markedly reduced in patients undergoing upper abdominal surgery when compared to those undergoing lower abdominal and lower extremity surgery.

The reason for attenuation but not total suppression of the metabolic response to injury in the face of epidural anesthesia with seeming adequate degree of neural blockade is due to a number of factors. It has been recently demonstrated that epidural lumbar[81] and thoracic[80] blockade with bupivacaine are unable to completely suppress the sensory evoked potentials from areas that appear to be clinically anesthetized. Another reason is that locally released humoral mediators (such as IL-I) may be stimulating the neuroendocrine axis, thus bypassing the central neural pathways.

Postoperative analgesia using epidural narcotics has become a popular technique for pain control. It has been observed that epidural narcotics do not suppress the endocrine and metabolic responses to the same degree as do epidural local anesthetics. This is probably due to the fact that neurogenic pathways other than the opiate-receptor dependent nocioceptive ones are important in mediating the stress response.[28,67] In some studies, patients administered epidural narcotics postoperatively had less of an increase in cortisol[110] and catecholamines[61] than did those given intermittent intramusclar narcotics, indicating that pain may play some role in the postoperative rise in these hormones. Downing and coworkers[45] observed that intrathecal morphine administered prior to surgery had no effect on the hyperglycemic response to surgery but attenuated the postoperative increases in cortisol.[28] Cowen and colleagues[37] observed lower levels of cortisol and glucose in patients given epidural diamorphine than those given epidural bupivacaine after total abdominal hysterectomy.

The reason some investigators found suppression of the metabolic response to surgery and others did not may be due to the type of anesthesia used during surgery and the dose and type of narcotic instilled into the epidural space. In some of the studies, epidural local anesthetics were used during surgery and thus may have an effect on postoperative responses.[67] It is possible that larger doses of epidural narcotics appear more able to suppress metabolic responses but also increase the complication rate from respiratory depression.

### Narcotic and Inhalational Anesthetics

Large doses of narcotics (morphine 4 mg per kg, fantanyl 100 μg per kg) given at the start (induction) of surgery can markedly suppress the increases in cortisol,[53,74,117] epinephrine,[74,93,106] norepinephrine,[74,93,106] aldosterone,[74] growth hormone,[53,96] beta-endorphin,[24] and vasopresson[24] observed during general anesthesia with volatile agents such as halothane. This attenuation of the stress response is also reflected by smaller increases in intraoperative plasma glucose[35,93] and lactate[102] concentrations. In many studies performed using such large doses of narcotics in patients undergoing open heart procedures, the suppression of the stress response was seen only prior to the cardiopulmonary bypass period.[74,102,106,117] In high doses, the newer analogs of fentanyl, sufentanil, and alfentanil appear to have similar abilities to suppress the hormonal responses,[16,42,43] although they have different pharmacokinetics.[15,68,90,107] In patients given high doses of morphine or fentanyl for operations not involving cardiopulmonary bypass, suppression of the stress response was observed throughout the time of surgery[24,93] and for at least the first three postoperative hours. The suppression of cortisol secretion appears to be centrally mediated since the administration of ACTH during morphine (4 mg per kg) anesthesia results in an increase in serum cortisol levels.[53]

The inhalational agents have served as the control anesthetics for studies of metabolic response suppression. This choice has been made because of the inability of most of these agents to affect the endocrinologic changes observed during surgery. High doses when compared with lower doses of halothane (1.2 versus 2.1 minimal alveolar concentration [MAC]) did not effect any change in blood glucose, lactate, glycerol, cortisol, insulin, or catecholamine concentrations during hysterectomy.[75] Some studies have indicated that enflurane may be better at preventing a rise in cortisol and ACTH prior to the surgical incision than halothane.[92] Compared with low dose fentanyl (0.33 ± 0.028 mg), nitrous oxide anesthesia, plasma norepinephrine, but not epinephrine, was lower in patients given enflurane (1 to 4 per cent), nitrous oxide anesthesia.[23] Supplementaion of nitrous oxide anesthesia with fentanyl (15 μg per kg) inhibited the increases in beta-endorphin, ACTH, growth hormone, and glucose concentrations observed in patients (pelvic surgery) receiving 0.5 per cent halothane supplementation.[57] It appears in most but not all cases,[1,51] that even in high doses, volatile anesthetics are unable to suppress the metabolic response to stress.

Long term infusions of the intravenous anesthetic induction agent, etomidate, has been associated with increased mortality in critically ill patients.[78] It has been shown that etomidate produces a concentration-dependent block of both the cholesterol side-chain cleavage enzyme and II-beta-hydroxylase. This results in marked suppression of plasma cortisol and aldosterone[52] with a resultant increase in plasma ACTH.[116]

The effects of anesthetic agents on systemic responses are dependent on the anesthetic agents and their route of delivery. It is still unclear whether using techniques that can alter the response to stress are beneficial in the short and long term. Yeager and coworkers[124] have recently reported that patients undergoing major vascular procedures given general plus epidural anesthesia had lower morbidity and mortality than patients given only general anesthesia. This matter still needs further study since some studies have reached other conclusions.[62,72]

### Adrenergic Agents

One of the major systems involved in the stress response is the adrenergic one. This consists of the sympathetic nervous system which uses norepinephrine as its neurotransmitter and the adrenal gland that secretes mainly epinephrine. There has been interest in the use of adrenergic blocking agents to alter the systemic responses. Beta blocking agents (propranolol) have been observed to reduce hemodynamic responses (blood pressure and pulse),[32] depress lipolysis,[95] attenuate the increase in blood glucose,[34] and lower plasma insulin levels.[118] Alpha adrenergic blockade with phentolamine caused an increase in plasma insulin and a decrease in the glycemic response in patients undergoing gynecological[27] and abdominal[59] surgery.

More recently there has been interest in the use of clonidine to suppress the sympathico-adrenal response to surgery. Clonidine is a centrally acting partial alpha-2 adrenergic agonist with antihypertensive and sedative properties. It reduces central sympathetic outflow and enhances vagal cardiac output. Patients undergoing coronary artery bypass grafting treated before and during surgery with intravenous clonidine had lower epinephrine and norepinephrine levels than control patients. Blood glucose, ACTH, plasma renin activity, and cortisol were unaffected.[50,59] Patients undergoing intraoperative controlled hypotension with intravenous clonidine had lower serum cortisol levels than did patients not given clonidine and not hypotensed.[85]

The modification, suppression, and attenuation of various portions of the adrenergic system appears to alter metabolic responses to surgical stress.

## Postoperative Responses

The period of time immediately following surgery is one of much stress. Emergence from anesthesia, extubation, and the trip to the recovery room or intensive care unit are all associated with much stimulation of the hormonal responses. Halter and colleagues[56] observed that during the perioperative period the highest levels of plasma catecholamines were observed immediately after surgery had ended. This is not unexpected, since this period of emergence from anesthesia and extubation of the trachea is associated with hypoxia and hypercapnia, both marked stimuli to activation of the sympathetic nervous system. Another potent stimulus to sympathetic activation is rewarming. Many patients suffer intraoperative hypothermia with temperatures decreasing to below 35°C. This is especially common in elderly patients, those undergoing prolonged operations, those undergoing operations that involve exposing large mucosal surfaces to the atmosphere, and those undergoing induced hypotension or cardiopulmonary bypass. The rewarming period after surgery is characterized by shivering, a stimulus that results in marked elevation of metabolic rate, heart rate, blood pressure, and serum catecholamine levels. In intubated, mechanically ventilated patients, shivering can be prevented by using muscle relaxants or large doses of narcotics.[97,98] In spontaneously breathing patients, meperidine has been reported to suppress shivering.[84] The importance of maintaining normothermia during surgery is underscored by the observation that elderly normothermic patients had less postoperative loss of nitrogen than hypothermic ones.[26] Pain, as well as emergence delirium, are also potent stimuli for sympathetic nervous system activation and release of the hormones associated with the stress response. It is, therefore, not unexpected that in many studies high dose narcotic anesthesia was very satisfactory in suppressing the intraoperative responses, but once the patients emerged from anesthesia there was no longer satisfactory attenuation of the response. Similarly, with epidural local anesthetics, the marked attenuation and even suppression of hormonal and substrate responses are often abrogated in the postoperative period. It, therefore, appears necessary to control not only the intraoperative but also postoperative activators of the stress response in order to achieve a continuous "stress-free" environment.

## Multiple Organ System Failure

Patients with multiple organ system failure have significant alterations in homeostatic responses. Unlike the patient undergoing elective surgery who has a self-limited injury inflicted during anesthesia and in whom hemodynamic aberrations are promptly treated, the traumatically injured patient frequently has a massive, diffuse injury complicated by uncontrolled shock. This situation leads to a hormonal and metabolic response that is often more severe than that seen during elective surgery. The septic patient is unique in that there is a continuous, uncontrolled, ongoing insult that serves as a constant stimulus to disordered homeostasis. The factors triggering this are usually not due to localized, well-defined processes as during surgical and traumatic injury, but to a systemic process that involves activation of many hormonal substances including monokines, lymphokines, prostaglandins, complement, and coagulation cascade. Therefore, altering the response to sepsis may be more difficult than altering the response to injury.

It is still unclear whether the observations made during attempts at suppressing and attenuating the responses to elective surgery are applicable to patients with multiple system organ failure. In a recent study, Shaw and colleagues[105] administered 0.5 per cent bupivacaine through a catheter located in the 6th, 7th, or 8th thoracic interspace to patients 1 to 5 days after major surgery or traumatic injury. They observed that in patients not receiving parenteral nutrition, there was a decrease in the turnover rates of both glucose and urea. When the blockade was instituted in patients receiving total parenteral nutrition containing high levels of glucose, there was also a fall in glucose turnover. The authors concluded that self-limited extradural blockade begun after surgery results in decreased gluconeogenesis with a resultant decrease in protein catabolism. Whether prolonged blockade of the disordered metabolism found after injury will provide similar suppression is unknown. In another study, Wolfe and coworkers[121] observed that the administration of the beta-adrenergic blocker, propranolol, to burn patients suppresses triglyceride-fatty acid cycling but not glycolytic-gluconeogenic cycling. Wilmore and colleagues[119] found that beta blockade alone or combined alpha and beta blockade decreased metabolic rate, minute ventilation, and free fatty acids in burn patients. The usefulness of using either epidural local anesthetic blockade or beta-adrenergic blockade to modify postinjury traumatic responses still needs further investigation. The major concerns about both methods are their hemodynamic effects: the vasodilation associated with epidural local anesthetics and the myocardial depression of the beta blockers. In addition, the disadvantages and advantages of altering homeostatic patterns are still unknown. The effects of suppressing only part of the stress response may result in unopposed reactions that may be detrimental; alternatively, selective blockade of potentially damaging mechanisms may be beneficial.

Whether the neuroendocrine and humoral mediator secretion can be attenuated and whether this attenuation is desirable is still unclear since the stress response has beneficial and detrimental homeostatic effects. The autocatabolism and disordered lipid and glucose metabolism are potentially detrimental, while the enhanced production of acute phase reactant, especially immunoglobulins, likely is advantageous. It is, therefore, important to consider that total attenuation of the response may not be desirable, but that only certain parts of the response should be altered. Since many of the "desirable" and "undesirable" responses are mediated by the same substances or groups of substances, selective blockade may be difficult. It also appears that the response to stress may be similar to other biological systems; like the irreversible course of events that transpire once the coagulation cascade is activated, the metabolic response may be difficult to control once initiated. This may thus complicate attempts to attenuate the responses to sepsis and accidental injury. Investigation of the biologic response to stress thus appears to be complicated by the complex interaction of the various physiologic and biologic processes. Ultimately one must remember that the benefits of fussing with "mother nature" are judged by the eventual outcome: mortality, morbidity, time of convalescence, length of hospital stay, and cost.

## PRACTICAL ASPECTS IN THE ANESTHESTIC MANAGEMENT OF PATIENTS WITH MULTISYSTEM ORGAN FAILURE

The previous portion of this article has dealt with the possible ways anesthetic techniques and drugs could modify the metabolic response to stress. Such modification has been performed on patients with single organ failure undergoing elective surgery. However, these observations may not be applicable to the patient with multisystem failure. The aim of the anesthetic management of patients with multisystem failure is to maintain and prevent any further deterioration in respiratory, circulatory, and renal function. In general, such patients require anesthesia for three types of surgerya: (a) infection control (drainage of abscesses or debridement of necrotic tissue); (b) reconstructive surgery (orthopedic stabilization, insertion and removal of hardware); and (c) life sustaining procedures (tracheostomy, insertion of peritoneal dialysis catheter and insertion of an arterial-venous shunt to facilitate hemodialysis). These patients usually have controlled airway (either tracheostomy or an endotracheal tube) and are receiving mechanical ventilation. They also usually have hemodynamic monitors such as arterial and pulmonary artery catheters. The controlled airway obviates the need for the traditional "induction" of anesthesia and allows for a slow and controlled institution of general anesthesia or the use of local anesthesia with sedation. It is important to use agents that will have minimal hemodynamic consequences, thus the heavy use of fentanyl and sufentanil in such patients. The addition of benzodiazepines should be viewed with caution since they may have a myocardial depressant effect when administered in conjunction with narcotics. Ketamine is frequently used with diazepan for short painful procedures, but its intrinsic myocardial depressant activity may result in hypotension in patients unable to mount the indirect release of catecholamines or who have marked cardiac dysfunction. Ketamine is also not indicated in patients with elevated intracranial pressure. Very low doses of volatile agents (0.125 to 0.25 per cent halothane or 0.25 per cent isoflurane) may also be considered as a supplement to narcotics and to provide amnesia. Muscle relaxants are often needed. It is essential that adequate sedation and anesthesia be maintained so that the patients are awake while paralyzed. The specific relaxant to be used and its dose must be considered in light of the underlying organ failures. For instance, metocurine or gallium should not be used in patients with renal failure while atracurium is the agent of choice. Fluid therapy should be guided by indwelling hemodynamic monitoring, preferably a pulmonary artery catheter. In general, anesthetic care of the patients with multiple organ failure requires that attention be paid to all body systems to prevent further deterioration.

## SUMMARY

Anesthetic agents and techniques can modify the systemic responses to surgical injury. Epidural blockade with local anesthetics in patients undergoing lower abdominal or lower extremity surgery can markedly attenuate the plasma levels of many of the stress hormones. It appears that it is more difficult to achieve comparable degrees of attenuation in upper abdominal surgery. Whether such techniques can be used in patients with multiple system organ failure to attenuate the autocatabolic processes is unclear.

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*Management of Patients with Multisystem Organ Failure* 0889–8537/88 $0.00 + .20

# Current Status of Multisystem Organ Failure and Possible Directions for the Future

*Christopher W. Bryan-Brown, MD**

Twenty years ago, those who were managing the critically ill with multisystem organ failure (MSOF) were frequently accused of treating patients without a diagnosis. It seemed obvious at the time that unless an assessment of the patient's physiologic deficits was made and efforts taken to correct them, that the patient would die or receive excessive damage to his body systems before a conventional pathologic or disease state could be diagnosed. Intensive care units became devoted to creating functional diagnoses and applying physiologic remedies in expensively and extensively monitored patients. Some improvements were seen in patient outcome, but overall, these were hard to document. Patients still continued, despite best efforts, to develop MSOF in spite of their highly tuned cardiorespiratory and even renal systems. It became obvious that patients in intensive care units were very prone to iatrogenic disease[19] and that the intensive care unit was a dangerous place to put a patient who was not critically ill. The philosophy of this system could be summed up as, "you treat what you see." As the data showing long-term benefits from all this monitoring and long-term therapeutic exercise has been sparse, there are several hypotheses that can be drawn from this experience in trying to prevent and treat MSOF: (1) The right variables may not be monitored. (2) The therapeutic support being given may either be misdirected or insufficient. (3) There is probably a lack of understanding of everything that needs treatment and which interventions are appropriate.

Whatever the causes of MSOF are (and there may be many), the definition of the problems and the prophylaxis or therapy will have to be worked out at the molecular level. The recognition that organ systems can fail because of remote tissue damage was already understood by workers in the field by the 1920s. Cannon[5] and later Moon[17] felt that the most significant mediators must be chemical and blood borne, while Crile[6] favored nervous pathways in his theories on "anoci-association." There is increasing evidence that both types of mechanism can play a part in the development of MSOF. If an injured part of the body is deafferented by regional anesthesia, some of the baneful remote effects may be moderated both by a reduction in stress-related endocrine secretion and a diminution of unnecessary sympathetic activity.[11,12] Monokines, such as Interleukin I, continue to have their effects, so that there is the generation of ACTH, fever, and phase reactant proteins (for example, fibrinogen and antiproteases), and the induction of various leukocyte functions. The stress response, both chemical and nervous, may produce advantages to compromised patients in the short term. With modern technology, the ability of the critical care team to prolong life under adverse circumstances can cause a continuation of the stress response well beyond initial resuscitation. The effects may be enhanced by the addition of exogenous sympathomimetic agents, which often appear to achieve a temporarily beneficial effect. When patients do not improve speedily, too frequently nothing more is gained than a postponement of death for a short while.

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## CARDIOVASCULAR SYSTEM

The avoidance and management of MSOF (with the exception of catecholamine administration) seems to be evolving into a systematic effort to "de-stress" the patient and administer the physiologic assistance needed to maintain organ function. Foremost is immediate circulatory resuscitation. The noxious stimulus (for example, sepsis, dead tissue, or hypovolemia) has also to be removed as soon as possible. Achieving the parameters of hemodynamics and oxygen transport and utilization best associated with survival has already been demonstrated to reduce the incidence of, and the mortality and morbidity from MSOF.[22,23] If critically compromised patients are given a blood volume slightly in excess of normal and their cardiac outputs are boosted by up to 150 per cent to maintain an oxygen uptake greater than 120 per cent of normal, survival is enhanced in traumatic, septic, and hemorrhagic shock.

In the mid-1970s Philip Lumb and I were investigating oxygen uptake in septic patients. It was puzzling how some patients, while being overcome by sepsis, would require greater and greater oxygen delivery (the product of cardiac output and arterial oxygen uptake) to increase or maintain oxygen uptake, as shown in the example in Figure 1.[4]

This data comes from an elderly male patient who had been in ill health following surgery for a perforated diverticulum of the colon. He had a fecal peritonitis for about a day before admission. Immediately after surgery he did well, but 48 hours later developed signs of septic shock and was hemodynamically monitored for the next 10 days until his demise. Initially, it was relatively easy to maintain ox-

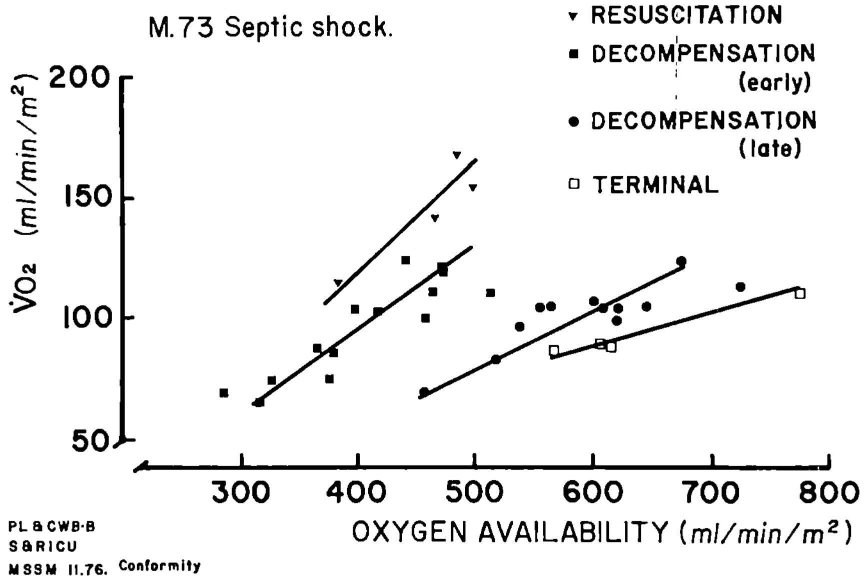

Figure 1. This oxygen uptake ($VO_2$) and delivery data from the final 10 days of a 73-year-old patient with MSOF developing following fecal peritonitis. Note that as the syndrome developed, ever greater oxygen availability was required to maintain oxygen uptake [9]. (Permission: The Society of Critical Care Medicine).

ygen uptake by the tissues, but this required a greater and greater oxygen availability until shortly before his death when 2½ times the initial oxygen availability was required to maintain the same level of oxygenation that he had when the monitoring was initiated. Some of his other data is shown in Figure 2, where the oxygen uptake was seldom even in the normal range. There was a gradual elevation of the venous oxygen tension to levels well above normal in the last 24 hours of his life. One of the seemingly paradoxical phenomena was that the lactate levels were in the low to normal range throughout the downhill course. While this patient was with a low oxygen uptake he did not develop lactic acidosis, as might be expected with MSOF.

This type of patient exemplifies many of the circulatory features of MSOF. It is tempting to ascribe a major part of the initial deficit to derangements in the microcirculation. Since the early work of Krogh,[13,14] it has been a premise that the increased metabolic requirements of a tissue can be met by increased extraction, increased blood flow through already open channels in the microcirculation, or the recruitment of capillaries previously in a no-flow state. There is range, from some tissues, such as myocardium, which have very little capacity for further oxygen extraction and are dependent on increased flow to provide the energy to meet an increased work load, to striated muscle, which appears to be able to use all mechanisms and is capable of extracting most of the oxygen in the arterial blood supply under heavy load conditions. During shock states a process

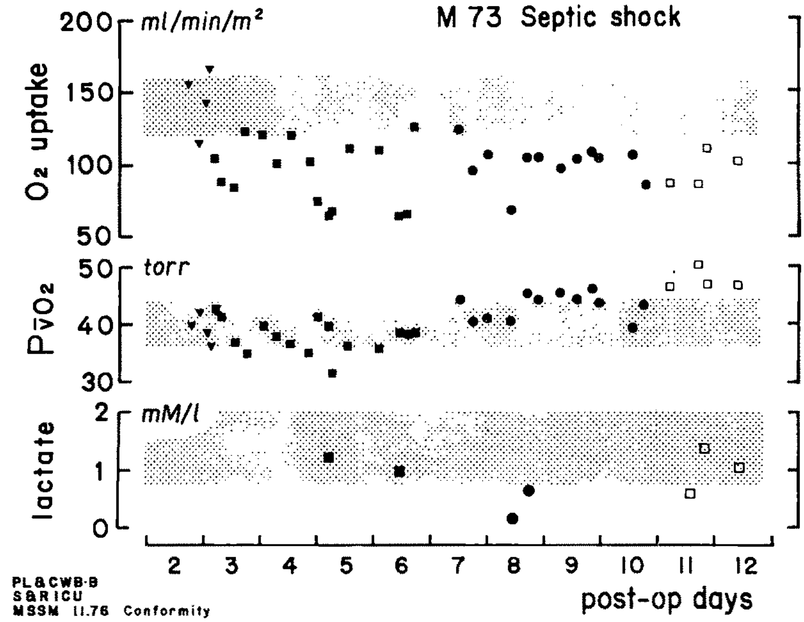

Figure 2. Data on oxygen uptake, mixed venous oxygen tension (PVO$_2$, and lactate concentrations from the same patient as in Figure 1. See text for details.

seems to be initiated that diminishes the delivery capacity of the microcirculation.[24] Capillaries may become plugged with activated platelets, increased activity of the complement system can cause leukocyte aggregation with microembolization as well as direct damage to the capillary endothelium. Eicosanoids such as thromboxane-$A_2$ cause microvascular constriction and local edema may cause further functional loss. Many of the cellular elements in a tissue are therefore removed a greater distance from their source of oxygen and substrate. As their metabolism begins to run down, they release vasodilators such as adenosine and hydrogen ion. These may vasodilate the open vascular channels in the tissues. As blood flow increases so does the gradient for oxygen and substrates between the capillary and the more distant cellular elements, providing a compensation that may give a better chance of survival. This mechanism will cause the oxygen tension to be high at the venous end of the microcirculation as the extraction ratio goes down with the increased blood flow. A greatly increased blow flow, therefore, may be needed to maintain oxygen delivery.

As it has become more evident that a considerable part of MSOF arises from a circulatory deficit in the microvasculature, the question is posed as to whether the current protocols of the management of the critically ill are as appropriate as their protagonists would claim. The usual monitoring systems give a host of directly measured and derived variables, many of which bear little on the patient's outcome,[22] but those related to oxygen transport and utilization seem to have most relevance to survival. Blood volume is measured in a very few centers, and can be found to be diminished far below the optimum amount for survival, even though there appears to be a normal set of hemodynamic data.[21] This should cause no surprise, as the physiologic mechanism that compensates for a low blood volume tends to maintain the most immediately necessary organs at the expense of those that can temporarily retire without immediate failure of the whole system.[3] It seems, therefore, very logical to resuscitate patients along the lines of the body's normal scheme, and maintain cardiac function and cerebral perfusion, even at such a cost. The relationship between circulatory pressures and blood volume was assumed to be such that an increased filling pressure of the ventricles must give rise to an increased ventricular volume, thereby stretching the myocardium and increasing the force of contraction. When cardiac work did not increase significantly in relation to elevations and filling pressure, the assumption was that the Frank-Starling curve had plateaued and that further volume loading would lead to cardiac failure. These ideas did not take into account increased myocardial stiffness due to sympathetic tone or hypoxia, nor the effect of increased sympathetic tone on capacitance vessels, which would give rise to a high filling pressure in the face of hypovolemia. The same sympathetic tone would maintain peripheral arterial blood pressure at the expense of splanchnic renal and cutaneous blood flow. The move toward the measurement of ventricular end diastolic volume during resuscitation and maintenance of unstable patients, is becoming more popular and would seem to be in the right direction. As volume resuscitation is administered, it is now possible to follow the ventricular size as a guide to the endpoints of fluid therapy and return to the true Frank-Starling relationship. The introduction of esophageal two-dimensional echocardiography[20] makes possible a direct measurement of ventricular size and also shows up changes in wall motion that may be due to ischemia. So far the apparatus is too bulky to be used routinely on the awake or noncomatose patient, but as it has already proved useful it will undoubtedly be miniaturized.

Boosting myocardial performance with exogenous adrenergic agents may continue the stress response for longer than is tolerable by many of the patient's systems. Vasopressors may indeed be required to maintain coronary perfusion, but do so at the expense of other systems. Using combined therapy with the addition of such drugs as dopamine may selectively maintain blood flow to the splanchnic area and kidneys. The art is to achieve the correct balance[18,25] that will increase cardiac output sufficiently to meet the needs of tissues without altering their blood supply so that they do not receive the benefit.

## THE MOLECULAR LEVEL

A large part of cellular metabolism is directed at maintaining the status quo that is life. Up to 60 per cent of energy expenditure may be used for preserving the normal intracellular concentrations of potassium and sodium.[10] Other ions also require pumping into or out of the cytosol. The most critical for cell survival appears to be calcium. The entry of small amounts of calcium is a necessity for cellular function, but it forever needs removing into the sarcoplasmic reticulum, mitochondria, and extracellular fluid. Excessive amount of calcium will activate phospholipases in the cytosol, which in turn will attack the phospholipids of the cell membrane, sarcoplasmic reticulum, and mitochondria, increasing their permeability and allowing yet more calcium into the cytosol. Phospholipase $A_1$ will also hydrolyze glyceride esters releasing arachidonic acid, thereby promoting the messengers of the eicosanoid system (prostaglandins, thromboxanes, and leukotrienes). This is well exemplified by the hypoxic model.[9] As oxygen is limited, ATP production decreases with the efflux of calcium from the cytoplasmic reticulum and through the mitochondrial membranes. With potassium efflux and sodium influx the cell membrane becomes increasingly depolarized until the voltage dependent gates of the calcium channels open. The influx of calcium is increased and the sodium-calcium pumping apparatus becomes less active. As there is increased hydrogen ion available from the breakdown of ATP, sodium is preferentially exchanged for hydrogen ion instead of calcium. Once a cell can no longer control the calcium ion it is "destined to die" (Britton Chance), even though specific functions may return. Attempts to control the entry of calcium into cells in order to prevent them becoming poisoned has been tried with various calcium channel blockers,[8] but there is no clinically relevant study to indicate that they would be of any use to alter significantly the outcome of MSOF. Many methods have been considered to cut down the permeability of cell membranes or to stabilize them against an attack by the ionophores that seem to be a key part in the spread of MSOF. It is possible in this manner to protect cell membranes to some slight degree. Oubain and furosemide have been shown to protect cells of the thick ascending limb of the loop of Henle in the renal medulla, which is probably the most sensitive area of the kidney to hypoxia.[2] These agents cut down ion transport mechanisms, and reduce energy requirements. It also has been shown that the toxicity of certain antibiotics in this region may be due to a nonspecific ionpohore effect. The increased permeability produced in the cell membranes results in an increased need for energy to maintain ion concentrations in the cytosol.[1] It would also explain why renal tubules are so sensitive to some nephrotoxic drugs during episodes of hypoxia and shock.

Cellular damage can, therefore, arise from external agents, which may increase cellular permeability to ions, which in turn increase the metabolic rate, as more energy is required to pump them back again. The double jeopardy, which may give rise to MSOF, is that at the same time microcirculatory alterations may reduce the supply of oxygen and substrate. The cell has to fall back on its limited energy reserves as ATP is not replaced by oxidative phosphorylation. There is a swing to anaerobic glycolysis, as ADP concentrations grow

(Pasteur effect). Substrate requirements become enormous. For instance, central nervous tissue doubles its glucose uptake when only 5 per cent of its energy is being generated anaerobically. Another major disadvantage of anaerobiosis is the production of toxic end-products, which then poison the cell. As creatine phosphate disappears, other reactions begin to take over. The myokinase reaction will synthesize a mole each of ATP and AMP from two moles of ADP. AMP is then either hydrolysed to adenine or deaminated to inosine monophosphate. Both these reactions are increased in the presence of increased hydrogen ion. Inosine can then be further deaminated to hypoxanthine, and this reaction reduces the nucleotide pool. There is then less material to build up to ATP should energy sources and oxygen return sufficiently to restore metabolism.

Another problem may arise when hypoxanthine is oxidized to xanthine by xanthine oxidase. This gives rise to free oxygen radicals, which can cause further membrane damage.[16] All these biochemical reactions lead to the question of the influence of substrate on cellular damage from other causes. Hypoxia from ischemia seems less damaging to the central nervous system than hypoxia from lack of oxygenation of the blood supply. High glucose levels make the cerebral damage worse. If substrate is readily available, and the mechanisms for oxidative phosphorylation are absent or markedly diminished, then the cells are likely to be compromised and depleted by a greater hydrogen ion concentration and free oxygen radical formation.

## POSSIBLE DIRECTIONS

The support of the critically ill patient when various organ systems have failed is basically a problem of intensive care logistics. No doubt there will be many improvements and refinements, but the principles are likely to remain largely unchanged. Questions will arise concerning the best ways to estimate or measure the blood volume, support the circulation, ventilate the distress lungs, maintain nutrition, manage the failed kidneys, etc. The answers will not materially affect what initiates MSOF or what can be done to arrest its progress or diminish its severity. There is a desperate need to find methods for restoring the immune system.

What little clinical data exists would indicate that the earlier and more complete the restoration of the circulation, the less ill the compromised patient will become.[22] Early warning systems are needed to alert the patient's attendants that something is coming amiss. While not all patients with peritoneal sepsis develop septic shock, they represent a high-risk group for MSOF. Cerebral function is frequently first noticed to deteriorate with quite small changes in effect. It should be investigated whether or not these early changes can be picked up sufficiently accurately by electroencephalographic analysis from changes in the spectral array. Other markers of incipient organ failure should likewise be looked for, as although most systems are usually damaged at the same time, overt failures may take a variety of times to develop.

Biochemical interventions, such as manipulations of substrate, may give cellular metabolism the margin needed to repair itself. Calcium channel blockers proliferate, and are still much under investigation as a possible means of maintaining cells damaged by oxygen lack. Various enzyme blockers are being considered. Allopurinol has been used to block xanthine oxidase, to reduce free radical production.[7] Free radical scavengers have been given to inactivate them before damage occurs. If the process is followed upstream, it might be beneficial to reduce AMP production by inhibiting the myokinase reaction. AMP is also generated by adrenergic stimulation. Studies are needed on the effect of blocking this, and on critically ill patients to ascertain the possible beneficial effects of exogenously administered catecholamines.

Various blockers and antagonists of other destructive agents, such as anti-inflammatory drugs, prostacyclin, and cogeners should have further trials. The search for "magic bullets" is bound to continue, but none have really provided the reversal of the whole syndrome, only of very small parts.

Two other modalities that are likely to be resurrected are hypothermia, which could hopefully reduce metabolic requirements to match energy production and, plasmapheresis, to remove toxic metabolites.

## CONCLUSION

The vast array of the cellular derangements of MSOF overcomes many patients and taxes the intellectual capacity of most physicians treating the condition. Once the cellular damage has reached a certain point, it may well be that the cell is "destined to die," and most of the therapeutic maneuvers do nothing more than given an opportunity for the less damaged cells to recover, and the patient to survive if enough organ function remains.

The current status of MSOF has changed little over the past few decades, but a better understanding of the mechanisms is giving us more therapeutic ideas to follow. The major thrust is still prevention, which is achieved by an immediate and full resuscitation of the circulation and oxygenation of the tissues, with the removal of noxious influences such as dead or severely damaged tissues and sepsis.

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*Management of Patients with Multisystem Organ Failure*

# Index

*Note:* Page numbers of issue and article titles are in **boldface** type.

Acute renal failure, **173–184**
  diagnosis of, 176–177
  etiology and prognosis of, 173–175
  nutrition in, 180
  pathophysiology of, 175–176
  treatment for, 178–181
Adrenal and thyroid dysfunction, effect on central nervous system, 215–216
Adrenergic agents, effect of, on systemic responses to elective surgery, 226–227
Adult respiratory distress syndrome (ARDS), parenchymal dysfunction as cause of, 138–139
Afferent neuronal stimuli, role of, in neuroendocrine response, 2–4
Amino acids, effect of, on ventilatory response, 64–66
Anemia, aplastic, critical care drugs associated with, in multisystem failure, 24
  hemolytic, critical care drugs associated with, 24
Anesthesia, epidural, effect of, on systemic responses to elective surgery, 222–225
  inhalational, effect of, on systemic responses to elective surgery, 226
Antidiuretic hormone, effect of, on neuroendocrine response, 16
Aplasia, factors leading to, in multisystem failure, 23–24
Arachidonic acid metabolites, for resuscitation in hemorrhagic shock, 130–131
ARDS. See *Adult respiratory distress syndrome.*

Biliary tract, dysfunction of, and multisystem organ failure, 193–194
Blood, for resuscitation in hemorrhagic shock, 128–129
Bowel, small, dysfunction of, and multisystem organ failure, 189–191
Brain, effect of hemorrhagic shock on, 123

Calcium metabolism, disorders of, effect on central nervous system, 214–215
Carbohydrate utilization, regulation of, in sepsis, 99–100
Cardiac failure, effect on central nervous system, 203–206
Cardiovascular dysfunction, in septic shock, **87–118**
Catecholamines, effects of, on metabolism, 9
  on neuroendocrine response, 6–10
  for resuscitation in hemorrhagic shock, 129
  for treatment of septic shock, 108
Central nervous system, effect of adrenal and thyroid dysfunction on, 215–216
  effect of cardiac failure on, 203–206
  effect of encephalopathy in pregnancy on, 210
  effect of endocrinologic disorders on, 211–215
  effect of hepatic failure on, 208–209
  effect of pancreatic encephalopathy on, 209–210
  effect of renal failure on, 206–208
Coagulation defects, correction of, in hemorrhagic shock, 131
Coagulopathy, as cause of chronic liver disease, 28
  as cause of liver disease, 27–28
  as cause of malnutrition, in multisystem failure, 28–29
  caused by liver transplantation, 31–32
  consumptive, in multisystem failure, 29–30
Colon, dysfunction of, and multisystem organ failure, 191

Dialysis, for treatment of acute renal failure, 179
Disseminated intravascular coagulation (DIC), acute, in multisystem failure, 30–31

Dopamine, for treatment of acute renal failure, 179
  for treatment of septic shock, 108
Drug metabolism, effect of nutrient infusion on, 66–67

EE measurement, interpretation of, in critically ill patients, 44–45
Efferent humoral response, role of, in neuroendocrine response, 4–18
Encephalopathy, complicating pregnancy, effect on central nervous system, 210
  pancreatic, effect on central nervous system, 209–210
Endocrinologic disorders, effect on central nervous system, 211–215
Energy expenditure estimation, from standard formulas, in critically ill patients, 43–44
Energy expenditure measurements, in critically ill patients, 41–43
Energy metabolism, in stress, 52–53

Fasted state, effects of nutrients on reversal of, 51–52
Fat metabolism, during oxygen deficiency, 104–105
  during stressed starvation, 53–54
Furosemide, for treatment of acute renal failure, 178–179

Gastrointestinal tract, effect of hemorrhagic shock on, 123
Glucagon, effect of, on neuroendocrine response, 13–14
Glucocorticoids, effect of, on metabolism, 7–8
Glucose metabolism, during stress, 53
Glucose transport, characteristics of, 98
Glucose utilization, effect of increased cardiac work on, 100–101
Growth hormone, effects of, on metabolism, 11
    on neuroendocrine response, 10–11

Heart, effect of hemorrhagic shock on, 121–122
  in sepsis, 89–105
Hematologic abnormalities, caused by septic shock, 80
Hematopoietic system, disorders of, in multisystem failure, 23–32
Hemofiltration, for treatment of acute renal failure, 179
Hemolysis, drug-induced, factors leading to, in multisystem failure, 24
Hemolytic uremic syndrome, and coagulation disorders, 31–32
Hemorrhagic shock, effect of, on neutrophil function, 33
Hemorrhage, response of body systems to, 120
Hemorrhagic shock, **119–134**
  and multisystem failure, treatment of, 125–131
  clinical assessment of, 123–124
  coagulation defects in, correction of, 131
  effect of, on brain, 123
    on gastrointestinal tract, 123
    on heart, 121–122
    on kidneys, 123
    on liver, 122–123
    on lungs, 122
  invasive assessment of, 124–125
  pathophysiology of, 119–121
  resuscitation in, 126–131
    arachidonic acid metabolites for, 130–131
    blood for, 128–129
    catecholamines for, 129
    fluids for, 126–129
    steroids for, 129–130
  treatment of, total parenteral nutrition for, 125–126
Hemostasis, abnormalities of, in multisystem failure, 27–32
  normal, 27
Hepatic failure, effect on central nervous system, 208–209
Hyperglycemia, effect on central nervous system, 211–212
Hypernatremia, effect on central nervous system, 212–213
Hyponatremia, effect on central nervous system, 213–214
Hypothalamic-pituitary-adrenal axis, effect of, on neuroendocrine response, 5–6
Hypoxia, effect on myocardial metabolism, 101–103

Immune system, alterations in, in multisystem failure, 32–35
Insulin, effect of, on metabolism, 13
    on neuroendocrine response, 11–13
Intravenous fat emulsions (IVFE), effects of, on lungs, in acutely ill patients, 63–64
Ischemia, effect on myocardial metabolism, 101–103

Kidneys, dysfunction of, caused by septic shock, 80
  effect of hemorrhagic shock on, 123

Lesions, of small bowel, and multisystem organ failure, 189–191
Levophed, for treatment of septic shock, 108
Liver, dysfunction of, and multisystem organ failure, 194–197
  caused by septic shock, 80
  effect of hemorrhagic shock on, 122–123
Liver disease, and coagulopathy, 27–28
  chronic, and coagulopathy, 28
Liver transplantation, and coagulopathy, 31–32
Lung injury, acute, hemodynamic abnormalities in, 142–144
  management of, 150
Lungs, edema of, effect of hemodynamics on, 140–142
  effect of hemorrhagic shock on, 122
Lymphocyte function, effect of trauma on, 33–34

Malnutrition, and coagulopathy, 28–29
Mannitol, for treatment of acute renal failure, 178
Metabolic brain disease, causes of, 205–206
Metabolic response, monitoring of, in multisystem organ failure, **39–47**
  to starvation, in acutely ill patients, 50
  to stress, in acutely ill patients, 52
Metabolism, drug, effect of nutrient infusion on, 66–67
  effect of glucocorticoids on, 7–8
  effects of catecholamines on, 9
  effects of glucocorticoids on, 6
  effects of growth hormone on, 11
  effects of insulin on, 13
  effects of neuroendocrine stress response on, **1–22**
  energy, in stress, 52–53
  glucose, during stress, 53
Multisystem organ failure, anesthetic techniques for modification of systemic responses in, **221–235**
  cardiovascular dysfunction in, **87–118**. See also *Septic shock, cardiovascular dysfunction in.*
  hematologic and immunologic abnormalities associated with, **23–37**
  hemorrhagic shock in, treatment of, 125–131
  hepatic and splanchnic response in, **185–202**
  management of patients with, **1–235**
  metabolic response in, monitoring of, **39–47**
  neurologic complications of, **203–219**. See also *Central nervous system.*
  pulmonary dysfunction in, **135–172**. See also *Pulmonary dysfunction, in multisystem organ failure.*
Muscle and plasma AA profiles, in acutely ill patients, 54–59
Myocardial metabolism, effects of ischemia and hypoxia on, 101–103
Myocardium, energy generation in, during sepsis, 96–98
  fuel utilization in, during sepsis, 98–99

Narcotics, effect of, on systemic responses to elective surgery, 225–226
Neuroendocrine stress response, metabolic effects of, **1–22**
  role of afferent neuronal stimuli in, 2–4
  role of efferent humoral response in, 4–18
Neutropenia, acquired, critical care drugs associated with, in multisystem failure, 25
  factors leading to, in multisystem failure, 24–25
Neutrophil function, effect of hemorrhagic shock on, 33
Nutrients, effect of, on reversal of fasted state, 51–52
  infusion of, effect on drug metabolism, 66–67
Nutrition, in acute renal failure, 180
  in acutely ill patients, **49–71**
  role of, in cell-mediated immunity, 32–33
  total parenteral. See *Total parenteral nutrition.*
Nutritional support, future aspects of, in acutely ill patients, 63–66
  in postoperative period, 59–62

Opiates, endogenous, effect of, on neuroendocrine response, 14–15
Organ failure, multisystem, management of patients with, **1–235**. See also *Multisystem organ failure.*
Oxygen deficiency, fat metabolism during, 104–105
Oxygen metabolism, disorders of, in septic shock, 88–89
Oxygen transport and utilization, abnormalities of, in multisystem failure, 144–147

Pancreas, dysfunction of, and multisystem organ failure, 192–193
Paralysis, muscle, for treatment of pulmonary dysfunction in multisystem organ failure, 162–163
Parenchymal dysfunction, and ARDS, 138–139
Pituitary-gonadal axis, effect of, on neuroendocrine response, 17–18

Pituitary-thyroid axis, effect of, on neuroendocrine response, 16–17
Platelet dysfunction, factors leading to, in multisystem failure, 26–27
Positive end-expiratory pressure (PEEP), in ARDS, 158–166
Pregnancy, encephalopathy complicating, effect on central nervous system, 210
Prostaglandin $E_1$, for treatment of pulmonary dysfunction in multisystem organ failure, 163
Prostaglandins, effects of, on lungs, in acutely ill patients, 63–64
Pulmonary dysfunction, in multisystem organ failure, **135–172**
    abnormalities of oxygen transport and utilization in, 144–147
    bedside hemodynamic measurements, 151–153
    clinical and pathologic correlations, 147–150
    effect of hemodynamics on lung edema and gas exchange in, 140–142
    hemodynamic management of, 153–154
    invasive hemodynamic monitoring in, 150–151
    muscle paralysis for treatment of, 162–163
    prostaglandin $E_1$ for treatment of, 163
    steroids for treatment of, 161
    ventilatory management of, 155–161

Renal failure, effect on central nervous system, 206–208
Renin-angiotensin system, effect of, on neuroendocrine response, 15–16
Respiratory muscle failure, in shock, 135–138
Resuscitation, in hemorrhagic shock, 126–131
Reticuloendothelial system, effect of trauma on, 33
RQ measurement, interpretation of, in critically ill patients, 44–45

Sepsis, early vs. late, in acutely ill patients, 61
  heart in, mechanics of, 89–95
    myocardial perfusion and metabolism of, 95–105
  pulmonary abnormalities associated with, 139
Septic shock, **73–85**
  cardiovascular dysfunction in, **87–118**
    effect on pulmonary circulation, right ventricle, and respiratory pump, 105–107
    management of, 107–108
    oxygen metabolism in, 88–89
  cardiovascular effect of, 75–80
  clinical manifestation of, 74
  diagnosis of and therapy for, 81–82
  organ dysfunction caused by, 80–81
  pathophysiology of, 74–75
  pulmonary damage caused by, 80
Shock, hemorrhagic, **119–134**. See also *Hemorrhagic shock.*
  respiratory muscle failure in, 135–138
  septic, **73–85**. See also *Septic shock.*
Starvation, in the nonstressed state, 50
  metabolic response to, in acutely ill patients, 50
  stressed, fat metabolism during, 53–54
  stressed vs. unstressed, 61
Steroids, for resuscitation in hemorrhagic shock, 129–130
  for treatment of pulmonary dysfunction in multisystem organ failure, 161
Stomach, dysfunction of, and multisystem organ failure, 186–189
Stress, glucose metabolism during, 53
  late, and multisystem organ failure, 62
  metabolic response to, in acutely ill patients, 52
Surgery, elective, systemic responses to, anesthetic modification of, 222–228
Surgical injury, systemic responses to, 221–228

Thrombocytopenia, critical care drugs associated with, in multisystem failure, 26
  factors leading to, in multisystem failure, 25–26
Thrombotic thrombocytopenic purpura (TTP), and coagulation disorders, 31–32
Total parenteral nutrition, for patients in hemorrhagic shock, 125–126
Transplantation, of liver, and coagulopathy, 31–32

Ulcers, stress, of stomach, role of, and multisystem organ failure, 186–189

$VCO_2$ measurement, interpretation of, in critically ill patients, 44–45
Ventilation, effect of amino acids on, in acutely ill patients, 64–66
Vitamin K deficiency, as cause of bleeding abnormalities, in multisystem failure, 28–29
$Vo_2$ measurement, interpretation of, in critically ill patients, 44–45

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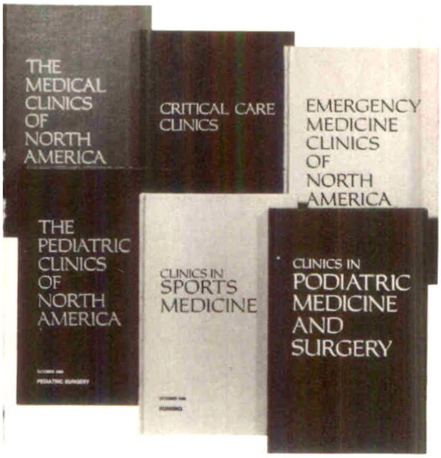
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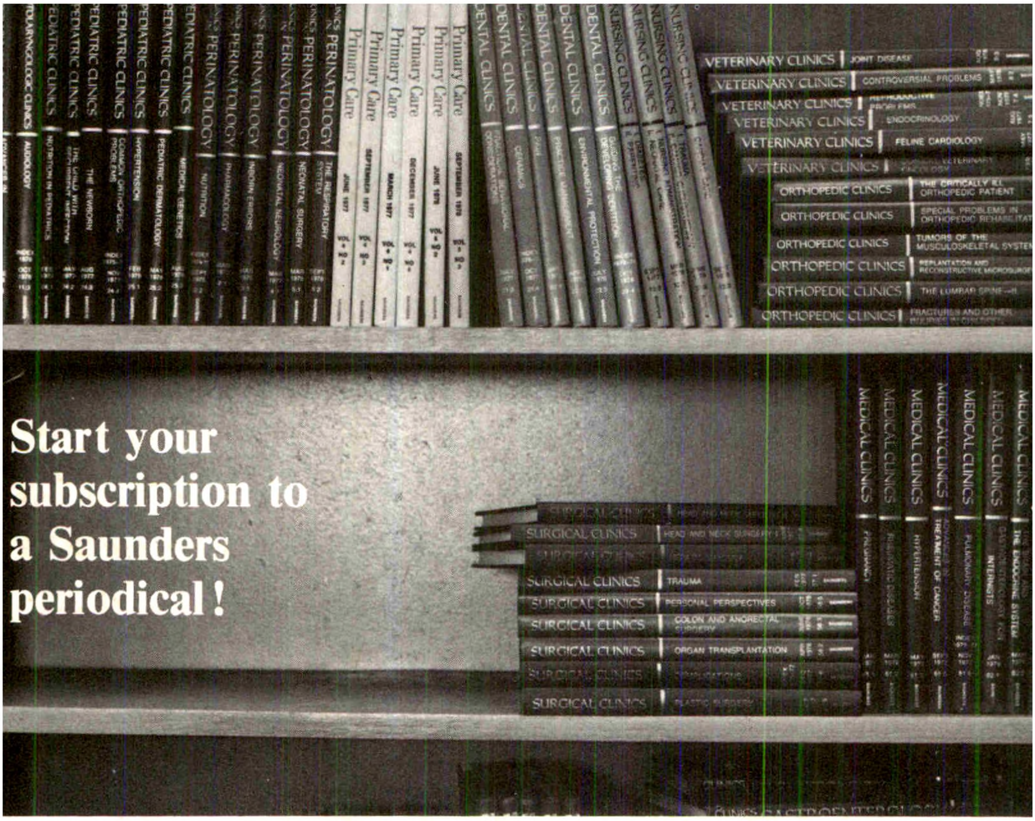

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